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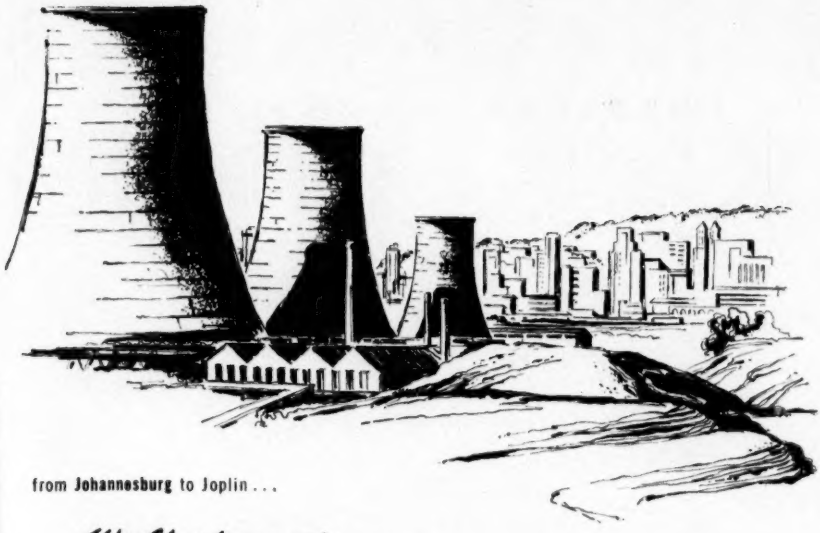

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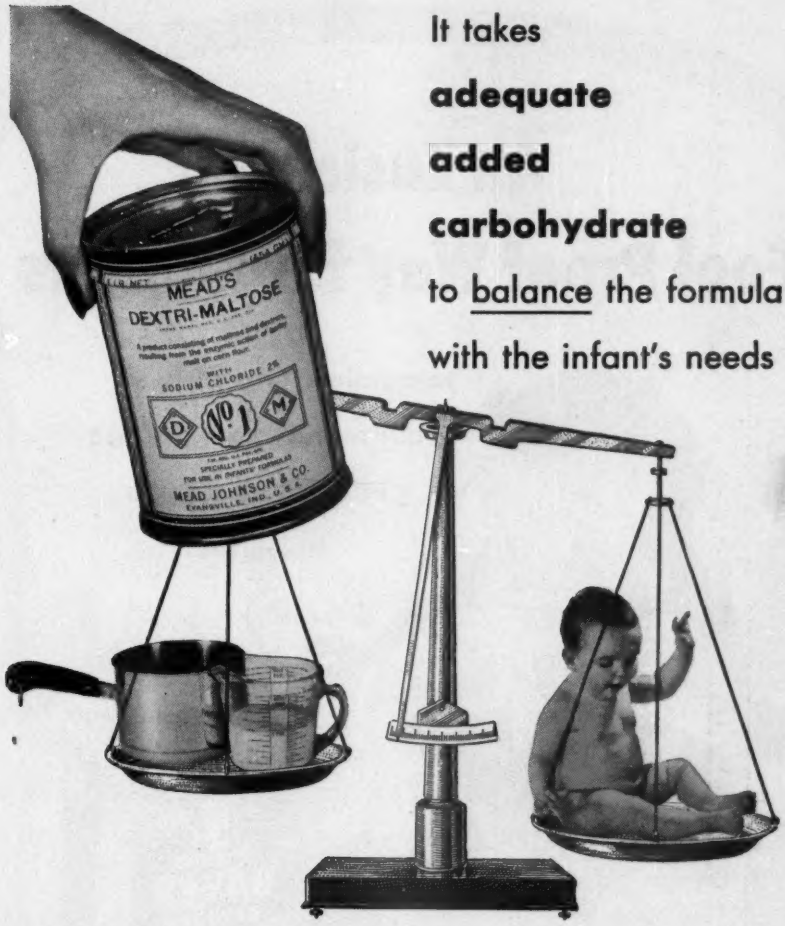

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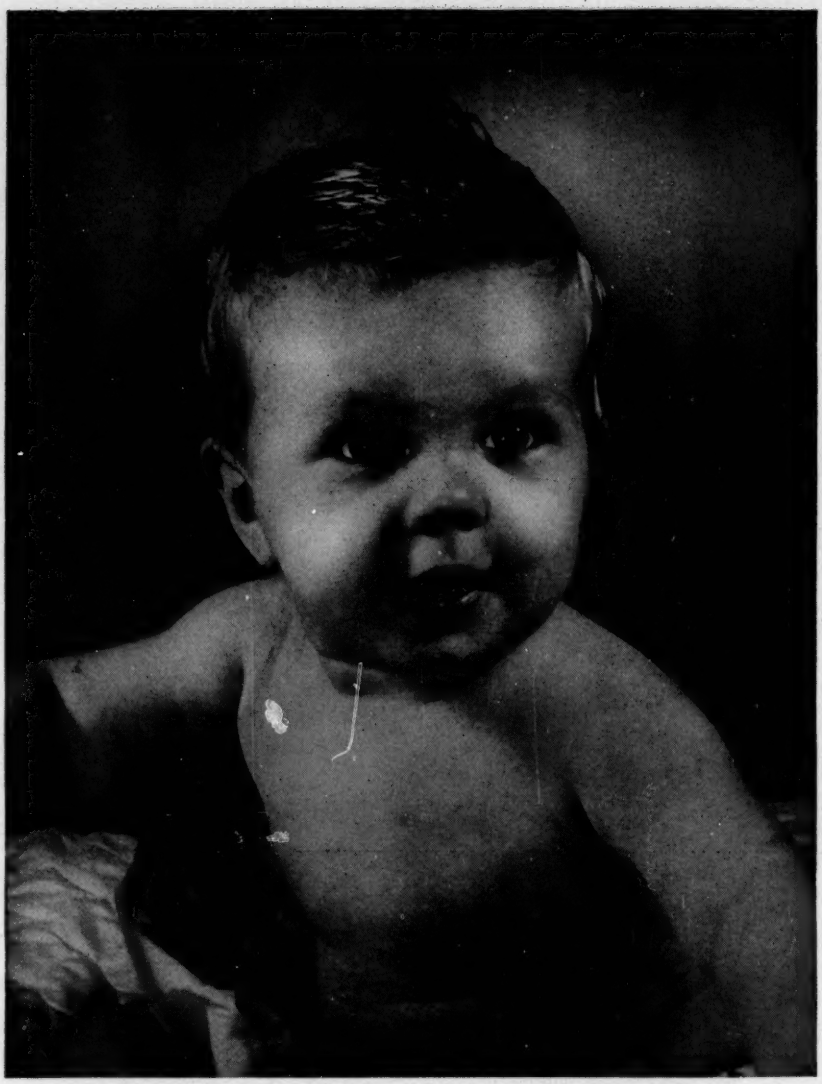

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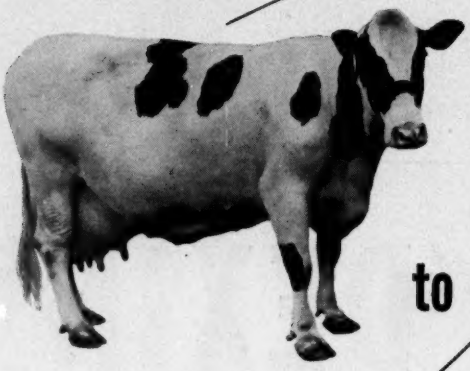

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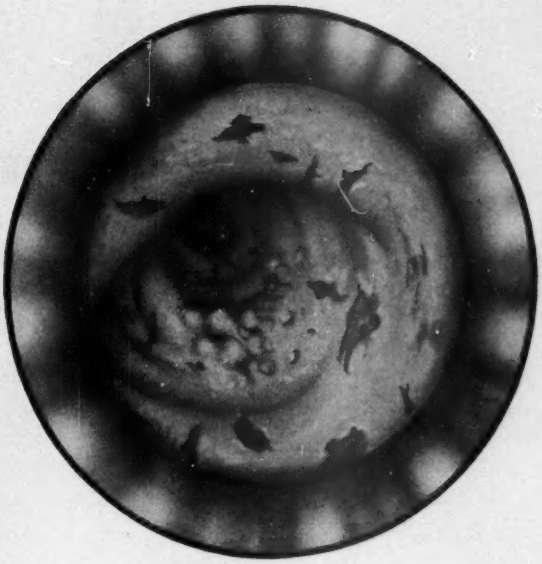

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1. Dowling, H. F., et al.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.

2. Sayer, R. J., et al.: Am. J. M. Sc. 221:256 (March) 1951.

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REFERENCES:

1. Bicknell, E and Prescott, F: The Vitamins in Medicine, 2nd ed., Heinemann, London, 1946.
2. Gordon, E. S.: Nutrition and Vitamin Therapy in General Practice, 3rd ed., Year Book Publishers, Chicago, 1947.
3. Jeans, P. C. and Marriott, W. McK.: Infant Nutrition, Mosby, St. Louis, 1947.
4. McLester, J. S.: Nutrition and Diet in Health & Disease, 4th ed., Saunders, Philadelphia, 1944.

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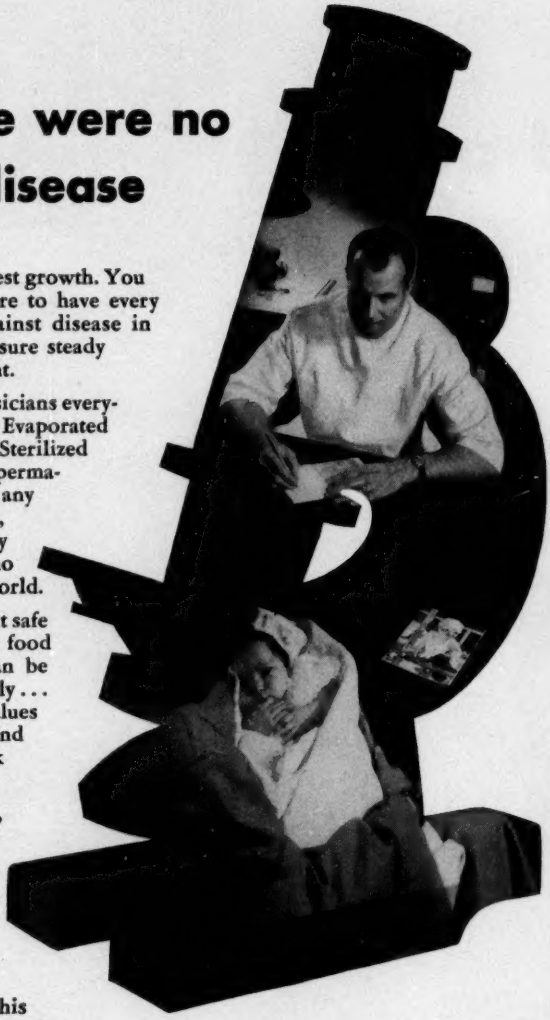

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EATING, SLEEPING, AND ELIMINATION PRACTICES OF A GROUP OF TWO-AND-ONE-HALF-YEAR-OLD CHILDREN

I. Introduction

KATHERINE E. ROBERTS, Ph.D.
AND
JUDITH A. SCHOELLKOPF, M.A.
ROCHESTER, MINN.

PURPOSE

THE ROCHESTER Child Health Institute is concerned with the well-being of children in the community, and essentially all the children of the community are available for developmental surveys.

This report is the first in a series of psychologic studies of children at different ages. The data on which this publication is based are part of a long-time psychologic research project designed to study the development of children in Rochester, where pediatric supervision is available to all children. The purpose of the present study is to investigate the eating, sleeping, and elimination practices of children aged 2½ yr., as reported by their mothers.

BACKGROUND OF THE STUDY

The Rochester Child Health Institute, established in 1944 under the leadership of the late Dr. C. Anderson Aldrich, is attempting in cooperation with other agencies to promote the physical and psychologic well-being of children. Part of the psychologic research program is concerned with the collection of data on the variety and significance of emotional problems in children and the determination of the types of facilities for prevention and treatment that can be developed in a community.

Rochester, Minn., is a town of about 30,000 inhabitants, located in the center of Minnesota's farming and dairy industry. It has a relatively homogeneous population, primarily white and of North European extraction. Most people live in single rather than multiple dwellings, and there are few extremes of wealth and poverty. The professional population is somewhat larger than would be expected in a town of this size, since Rochester is the site of the Mayo Clinic.

From the Rochester Child Health Institute. (The Rochester Child Health Institute was disestablished on July 1, 1951.)

The late Dr. C. Anderson Aldrich gave encouragement and support to this study; the staff of the Rochester Child Health Institute gave suggestions and criticisms. Dr. Arthur Steinberg served as statistical consultant.

The Rochester Child Health Institute has received Grants-in-Aid from the Mayo Association, the Field Foundation, the Schlitz Foundation, Mead Johnson & Company, and the Federal Security Agency. The grant from the Field Foundation was made primarily for the support of psychologic studies.

About 97% of the babies born in Rochester during the years 1944 through 1946 were born at St. Marys Hospital, and about 95% were registered in the Well Child Clinics. The plan is that each child in the first year of life attend the Well Child Clinic once a month; from 12 to 18 mo. of age, every two months; from 18 to 24 mo., every three months, and after 2 yr., every six months. Extra visits are arranged as necessary. As in other communities, sick children are cared for by physicians in private practice.

METHODS

The data for the study of children aged 2½ yr. are based on interviews with mothers and observations of children in a testing and unstructured play situation. The test used was the Revised Stanford-Binet, Form L. Specially constructed record blanks (Figs. 1 and 2) served as flexible guides for the interview with the mother and observations of the child. This first study of children aged 2½ yr. makes use of only part of the interview data and none of the test data.

About two weeks before the child attained the age of 2½ yr., each mother was sent a letter informing her that developmental tests would be given to all children aged 2½ yr. in Rochester whose parents were interested. A definite appointment date and time were given, and a return card was enclosed for the acceptance or refusal of the appointment. If a reply was not received promptly, a second letter was sent or a telephone call was made, for every effort was made to get the cooperation of the parents.

Two psychologists worked together, one with the child and one with the mother. About an hour was planned for each appointment, and adequate time was allowed for rapport to be established before the interview with the mother and the test and play session with the child began. Most of the children were able to leave their mothers and go alone for the test, but if a child indicated that he needed his mother, she accompanied him and remained with him as long as necessary. Incomplete interviews were finished when the mother returned for her second visit. In all cases mothers were invited to return for a follow-up conference to discuss the interpretation of the test results and the child's developmental progress. If the problems were such that further help was needed, the possibilities of referral were discussed, and in some cases appropriate referrals were made. These referrals included the Well Child Clinic, the nursery school, the pediatrician, psychiatrist, social worker, nutritionist, or psychologist. It must be kept in mind that these parents were invited to bring their children for a check-up and did not come primarily because they recognized a need for guidance. Since treatment facilities for young children are as limited in Rochester as elsewhere, most of the children referred were those whose mothers recognized a need for change in themselves or their child. Those children who remain in Rochester can be studied at later ages, and their development can be evaluated in relation to whether their early problems were recognized and treated or were left untreated.

SUBJECTS

Of the 1,048 parents who were invited to bring their children for the developmental test, 929 (88.6%) accepted the invitation and 119 (11.4%) refused it. The 929 who came will be designated as the "acceptance group" and the 119 who did not come as the "refusal group." When the two groups were compared according to the number of clinic visits during the first two years of the child's life, it was found that the average number of visits was significantly higher ($p<0.001$) for the acceptance group than for the refusal group. The average for the acceptance group was 11.3 visits and for the refusal group 6.6 visits.

It would seem that the parents who did not bring their children for the test were those who had a tendency to seek less service for their children through the Well Child Clinics than the parents who brought their children for the test. Those who took advantage of frequent visits to the clinics likewise accepted this additional

ROCHESTER CHILD HEALTH INSTITUTE

Preschool Clinic: Record at 2½ Years

CLINIC NO.....NAME.....

ADDRESS.....SEX.....

BIRTHDATE.....BIRTHPLACE.....CLINIC: City Hall.....St. Marys.....

DATE.....AGE.....

HEIGHT (in.).....WEIGHT (lbs.).....BI-ILIAC DIAMETER (cm.).....

EYES.....EARS.....

NOSE AND MOUTH.....TONSILS.....

TEETH: Occlusion.....Caries.....Other defects.....

HEART.....LUNGS.....

ABDOMEN.....GENITALIA.....

EXTREMITIES.....FEET (Describe).....

POSTURE (1-4).....NUTRITION (1-4).....

SKIN.....OTHER DEFECTS.....

SUGGESTIONS.....

SKIN TESTS (type, date, reaction).....

IMMUNIZATIONS (since last examination).....

ILLNESS, INJURIES, ETC. (since last examination)

Diagnosis	Date of onset	Diagnosis	Date of onset
.....	.....	.....	.....
.....	.....	.....	.....
.....	.....	.....	.....

MISCELLANEOUS (adopted, twin, boarder, etc.).....

.....

DATE.....BIRTHDATE.....AGE.....

EATING HABITS

Eats alone.....with family.....No. at table: Children.....Adults.....

Amount of food.....Variety.....

Food between meals: When.....What.....

Family eating habits.....

.....

Methods used by adults: Ignore.....Bribe.....Child serves self.....Coax.....

Clean plate.....Help.....Play games.....Praise.....Prescribed order.....

Punish.....Suggest.....Other.....

.....

Agreement of adults.....

Problems: Yes.....No.....

Suggestions.....

SLEEPING HABITS (1-4)

Night: Asleep.....Awake.....

Nap: Regular.....Irregular.....Length.....

Sleep where.....

Quality of sleep: Quickly asleep.....Calm.....Restless.....

Night terrors.....

Awakening: Happy.....Irritable.....

Bedtime ritual.....

Problems: Yes.....No.....

Suggestions.....

ELIMINATION: BOWEL

Frequency.....Regular.....Irregular.....

Responsibility.....

Constipation.....Frequency.....Control.....

Problems: Yes.....No.....

Suggestions.....

Fig. 1.—First and second pages of record blank.

ELIMINATION: BLADDER

Frequency (daytime)..... Responsibility.....

Wets self (day)..... Conditions.....

Wets bed (night)..... Frequency.....

Wets bed (nap)..... Frequency.....

Taken up at night.....

Problems: Yes..... No.....

Suggestions.....

DISCIPLINE: Easy to manage..... Difficult to manage.....

Methods.....

REACTION TO PEOPLE OUTSIDE FAMILY: Adults (1-4)..... Children (1-4).....

Contacts.....

ATTENDS NURSERY SCHOOL..... CHURCH SCHOOL (where).....

PLAY: With whom..... Ages.....

Where.....

Equipment.....

Relationships.....

HANDEDNESS: R..... L..... A..... Activities.....

ENERGY OUTPUT (1-4).....

LANGUAGE: Amount..... Quality.....

Problems.....

EMOTIONS: Predominant mood..... Variation.....

Fears.....

Conflicts.....

EXPRESSION OF POSSIBLE TENSION:	Often	Occasionally	Rarely	Never	Remarks
Thumb or finger sucking					
Nailbiting					
Hair twisting, pulling, patting					
Rocking					
Masturbation					
Crying					
Whining					
Blinking					
Negativism					
Stuttering					
Temper tantrums					
Others					

CHARACTERISTICS OF CHILD:	Inquiring	Imaginative	Resourceful	
Affectionate	Sensitive	Tense	Calm	
Cries easily	Independent	Belligerent	Cooperative	
Anxious	Dependent	Humorous	Laughs readily	
Withdrawn	Stubborn	Friendly	Irritable	
CHARACTERISTICS OF PARENTS:	Affectionate	Cooperative	Calm	
Tense	Friendly	Defensive	Anxious	
Resourceful	Talkative	Enthusiastic	Understanding	
Over-protective	Dominating	Satisfied	Humorous	

Fig. 2.—Third and fourth pages of record blank.

service. The actual reasons given for not bringing the children can be classified under various headings such as difficulties in making arrangements for the care of other children, illness, lack of interest, lack of time due to mother's working hours, or in some instances a genuine feeling that their children's progress was satisfactory and they did not need this service.

Data on mothers' education were available on only a part of the sample, since this question was not asked in the beginning of the project. It seems reasonable that the 232 mothers for whom these data were available are representative of the total group of 783 on which this study is based. The table indicates the frequency of highest educational level attained for the acceptance and refusal groups.

The two groups clearly differ in the proportion of mothers who attended grade school only and in the proportion who attended college. Although the 36 mothers in the refusal group constitute 16% of the total group of 232, the distribution of the acceptance group agrees closely with that of the total group. It may be validly concluded, then, that the mothers who accepted the invitation are representative of the Rochester population as a whole, so far as educational level is concerned.

The study reported in the following pages is based on 783 of the 929 children in the acceptance group. The 146 children not included in this study are those

Educational Level of Mothers in Acceptance and Refusal Groups

	Acceptance Group		Refusal Group		Total	
Educational Level	No.	%	No.	%	No.	%
Grade school	20	10.2	10	27.8	30	12.9
High school	121	61.7	24	66.7	145	62.5
College	55	28.1	2	5.5	57	24.6
Total	196	100.0	36	100.0	232	100.0

whose records were incomplete. The incomplete records were of two kinds, early forms of the record blank and those taken by an untrained interviewer.

The age range of these 783 children was from 29 to 31 mo. inclusive, most of the children being 30 mo. Of the 783 children, 360 (46%) were boys and 423 (54%) were girls. The average IQ was 114, the range being from 63 to 163. Seventy-two per cent of these children were born in Rochester, and 28% were born elsewhere.

Only data from the first four sections of the interview blanks have been used in this study, but other studies will follow, making use of the additional material obtained in the interview with the mother and the observation of the child.

The averages presented in this study should not be considered as norms for all children aged 2½ yr. They are based on a representative sample of Rochester children whose mothers have been guided by pediatricians in the Well Child Clinics. There is no control group with which to compare this guided group, since almost all of the children in Rochester are registered in the Well Child Clinics.

By the age of 2½ yr., most children in our culture are expected to have solved the problems of the oral phase of development, to be comfortably in control of those of the anal phase, and to be making progress toward mastery of the third phase, the urethral. If the problems of each period are satisfactorily resolved, energy is freed for subsequent stages of development. This preoedipal age of 2½ yr. seems to be a

good time to observe and study the ongoing process of development, and much more documentation is needed on the way in which these early phases of development contribute to the formation of personality structure.

This study will be presented in four sections: (1) eating practices, (2) sleeping practices, (3) elimination practices: bowel, (4) elimination practices: bladder. While each aspect of development is presented separately for purposes of organization, all need to be considered together if their significance in the life of a child is to be understood.

The reader should keep in mind that the data were obtained through interviews with mothers and are subject to all the limitations inherent in this method. The results are based on mothers' reports rather than on records made by special observers and represent what the mothers said was true of their children.

The question will undoubtedly be asked as to the mother's need to give answers that are compatible with the known philosophy of the Child Health Institute. In a sampling of 783 mothers, there were, of course, all degrees of freedom and inhibition in discussing their children, but an effort was made by the interviewer to give the mothers the feeling that there were no right and wrong responses. Since this sampling represents a cross section of Rochester mothers, there are probably some who described their children as more ideal than they actually were and others who painted a blacker picture of their children than was actually true. We are well aware of this tendency as a criticism of this type of study, but nothing short of deep analysis with careful documentation would control this factor.

EATING, SLEEPING, AND ELIMINATION PRACTICES OF A GROUP OF OF TWO-AND-ONE-HALF-YEAR-OLD CHILDREN

II. Eating Practices

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THE PARENTS of the children used in this study have been exposed to an educational program designed to help them understand the developmental process. Discussions about feeding are begun in the prenatal clinics, where mothers are instructed about their own diets. The mothers are helped to get a working knowledge of nutrition so that they can prepare and eat a diet adequate for the growth of the baby and for breast feeding if they so desire. The values for mother and child of breast feeding are discussed, but physicians, nurses, and nutritionists try to leave the mother feeling that she is the one to choose whether her baby will be breast-fed or bottle-fed.

Leaflets, given to the mother in the hospital, explain the baby's regimen in the newborn nursery and attempt to convey the idea that a baby needs to eat when hungry and that a mother can help by finding the most suitable schedule for her particular baby.

Each time the mother comes to the Well Child Clinic, the baby's progress in eating is discussed and his readiness for the next step is observed. New foods are added as the physician thinks wise, and the mother is helped to understand and value the child's progress. She is advised to find out what essential foods the child likes and serve him these foods often, to introduce new foods gradually, to avoid forcing and nagging, and to create a pleasant atmosphere for eating.

Under this regimen many mothers seem able to be tolerant of their child's needs and peculiarities and to let him progress at his own rate. However, there are some mothers who are anxious about the amount and variety of food the child eats and who cannot keep from showing their apprehension. Such mothers need special help from the pediatrician, and undoubtedly some of them later will seek psychiatric advice for feeding and allied problems.

The main emphasis in this study of eating practices is on psychologic rather than nutritional factors. Eating is one of the earliest experiences through which the mother-child relationship becomes established, and it continues throughout life to reveal the quality of this as well as other emotional relationships. In infancy and early childhood particularly, the eating situation is a delicate barometer of physical and psychologic disturbance or well-being.

From the Rochester Child Health Institute. (The Rochester Child Health Institute was disestablished on July 1, 1951.)

In the interview, mothers were asked questions that were intended to reveal the atmosphere at mealtimes, the likes and dislikes of the family members, the attitudes about food and eating prevalent in the family, the methods used in the management of the children, the mother's estimate of the amount of food eaten by the child, and the mother's satisfactions and complaints about the child's eating.

At the age of 2½ yr., these 783 children were eating three regular meals a day and most of them (93%) had additional food between meals. This practice is in agreement with the opinion of some nutritionists who believe that children are more adequately nourished and are less fatigued and irritable when fed oftener than three times a day. Most of these children (94%) ate their meals with the family rather than alone or with siblings or maids.

It is a well-known fact that children vary in the amount of food they eat. In this study mothers were asked to classify their children according to whether, in the mother's opinion, they usually ate a small, moderate, or large amount of food. Since some mothers were unable to say that their children usually belonged in one of these three groups, a fourth category, variable, was added. Table 1 gives the results.

TABLE 1.—*Mothers' Reports of Amount of Food Eaten by Their Children*

	Boys		Girls		Total	
Amount of Food	No.	%	No.	%	No.	%
Small	52	14.5	104	24.6	156	19.9
Moderate	113	31.5	141	33.3	254	32.5
Large	113	31.5	94	22.2	207	26.5
Variable	81	22.5	84	19.9	165	21.1
Total	359	100.0	423	100.0	782	100.0
Not stated	1				1	
$\chi^2 = 17.12$		$n = 3$		$p < 0.001$		

About a third of the children (32.5%) were considered by their mothers to eat a moderate amount of food; 19.9% ate a small amount; 26.5% ate a large amount, and 21.1% ate a variable amount. There is a statistically significant difference between boys and girls in the amount of food eaten as estimated by the mothers. More girls than boys were reported to have a small food intake, whereas more boys than girls were reported to have a large food intake. It should be remembered that the food intake of these children was not actually measured but that the data tabulated represent rather the mother's estimate of the amount eaten. Since there is no clear-cut evidence [1] for differing food requirements in boys and girls at this age, the mothers' estimates were probably influenced by psychologic factors. Are these differences a manifestation of the mother's expectation that boys should be larger eaters than girls? Is it a mark of femininity to be a dainty eater and of masculinity to be a hearty eater?

1. Breckenridge, M. E., and Vincent, E. L.: Child Development; Physical and Psychological Growth Through the School Years, Ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 157. Sherman, H. C.: Chemistry of Food and Nutrition, Ed. 8, New York, The Macmillan Company, 1949, p. 171. Talbot, F. B.: Basal Metabolism in Children, in McQuarrie, I.: Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 1, Chap. 22, p. 10.

Most children show variations from time to time in their eating practices. The appetite is easily affected by illness, emotional upsets, climatic changes, or any threat to the organism. When these deviations are transitory, there is usually no cause for undue concern. However, when the deviations are persistent and are based on an underlying emotional conflict, there is cause for concern, for these deviations in eating practices are symptomatic of relationships that are not conducive to good mental health.

Pediatricians, nutritionists, and psychologists are frequently consulted about feeding problems. Some of these problems are easily solved on a superficial level, while others are of a more serious nature and need deeper treatment. English and Pearson [2] wrote, "Emotional disorders of appetite, ingestion and digestion of food are very common in children, constituting about 24 per cent of all pediatric cases. . . ." Many of the mothers in this study of children aged 2½ yr. (82.6%) accepted their children's eating practices as satisfactory, but 17.4% of the mothers gave evidence that pointed to some disturbance related to eating. In some cases

TABLE 2.—*Number and Percentage of Children with Various Types of Eating Problems*

Problems	Children	
	No.	% *
Finickiness	78	10.0
Voraciousness	2	0.2
Bottle still used	25	3.2
Refusal to swallow certain foods	6	0.8
Child fed by parent	10	1.3
Preference for baby foods	2	0.2
Misbehavior at table	10	1.3
Others	3	0.4
Total	136	17.4

* Percentages based on total group of 783 children.

the mothers complained about the child's eating practices or said, "That's my problem," when questioned about the child's eating. In other cases the mothers described their child's behavior in such a way that the interviewer classified it as a problem even though the mothers did not express overt concern.

Table 2 gives the incidence of the various types of eating problems. Each of the 136 children in the problem group was classified according to the predominant problem.

The problem having the highest incidence was food finickiness, 10% of the total group of 783 children being in this category.

It will be noted that many of the children described as small eaters in Table 1 are not included as problems in Table 2, for many mothers accept small appetites as normal for their children at this age. Some of the finicky children needed close supervision by a physician or nutritionist, for the amount of food consumed was actually small and limited in variety. However, many of these children who were called finicky eaters appeared to be well-nourished and according to the currently

2. English, O. S., and Pearson, G. H. J.: Common Neuroses of Children and Adults, New York, W. W. Norton & Company, Inc., 1937, p. 83.

accepted growth standards, physically healthy; in these cases it seemed to be the mothers' anxiety that prompted them to report and treat their children as presenting eating problems.

The data for boys and girls are not reported separately, since no statistically significant sex differences were found in the incidence of eating problems. It will be remembered that the results given in Table 1 showed that there were more girls than boys who had a small food intake. Yet in the category of finickiness, for which small food intake is part of the problem syndrome, there is no difference in the percentage of boys and girls showing this problem. Perhaps the difference is obscured. In the 78 children listed as finicky eaters in Table 2, 31 are boys and 47 are girls. These 31 represent 60% of the boys whose mothers reported a small food intake, and the 47 girls represent 45% of the group whose mothers reported a small intake. It looks as if there is a tendency for mothers to be more concerned over small food intake in boys than in girls. This may be due to the fact that in our culture large food intake is often symbolic of masculinity.

In this group of 783 children, only two (one boy and one girl) were considered voracious eaters. Either overeating at this age does not often occur, or mothers were not sufficiently anxious over it to report it. It will be interesting to study at what age obesity and compulsive eating occur with greater frequency and to see whether or not these two children will be among those severely affected.

Not all mothers of children who still drink milk from a bottle at this age manifested anxiety about it, although the majority questioned the reason for the child's need of a bottle and the advisability of letting their children continue with it. However, this prolonged clinging to the bottle ranked second among the eating problems, being present in 3.2% of the total group of 783 children. It was noted that some of these children still drinking from a bottle showed immaturity in other areas, such as needing excessive rocking to sleep, lack of bowel or bladder control, and general overdependence in their relationship with one or both parents. In some cases the 2½-yr.-old child reverted to the bottle at the birth of a new baby, but in the majority of cases the child had never given it up. The significance of needing a bottle at this age when most children have given it up is not clear. It may indicate anxiety in the parent-child relationship and may be symptomatic of a fear of growing up. A special study of these 25 children is needed to clarify this issue.

Six mothers had as their chief complaint their child's refusal to swallow certain foods. One mother reported that her child liked only milk and soft foods, such as pancakes, spaghetti, canned fruit, and bananas. He would chew meat but spit it out instead of swallowing it. He was coaxed, bribed, and helped and was so restless he could not sit through a meal. This type of eating problem seems to reflect an impaired parent-child relationship. Five of the six children included in this category were found to have exceedingly hostile relationships with their parents.

There were 10 children in the study who were partially or almost entirely fed by their mothers. In some of these cases it seemed to be determined by the mother's previous forcing of the child, by her own desire to speed up eating or to prevent messiness. In other cases the child was insisting on being fed, and the mother was complying with the child's demands, some of which were precipitated by jealousy of a new baby.

Two mothers reported that their children preferred baby foods as their principal diet, and 10 mothers presented misbehavior at the table as being a problem. In those cases in which the mother complained of her child's behavior at table, the family seemed to have unusually rigid and perfectionistic standards. In one family, for example, the father insisted on absolute silence at mealtime; in another, spilling or messiness was intolerable to the adults.

Three children could not be placed in any of the foregoing categories. One child frequently gagged and vomited, while another showed excessive fear of spilling of milk or of being messy. The third child, who complained of a pain in his stomach, required a drink of milk every half hour and vomited every other day, appeared to be identifying himself with his father, who had an ulcer.

This survey of 783 children has pointed out some of the types of eating disturbances that occurred in a sampling of 2½-yr.-old children in Rochester. Eating problems are familiar to the pediatrician and to the staff of any well child clinic, for they are one of the commonest means by which the infant and preschool child react to the major or minor changes of their lives. In some of the 136 children with eating problems the problems were transitory and mild. In many of these children, however, they were symptomatic of varying levels of disturbance in the parent-child relationship. Complete case histories would need to be presented and all available information studied in order to understand the full significance of the symptoms in these children.

SUMMARY

Of the 783 children used in this study, 93% ate between meals.

The majority of the children (94%) ate with the family.

More girls than boys were reported by their mothers to have a small food intake. More boys than girls were considered to have a large food intake.

Many of the mothers (82.6%) accepted their children's eating practices as satisfactory, but 17.4% gave evidence that pointed to some disturbance related to eating.

Food finickiness had the highest incidence of any problem, 10% of the group of 783 children showing this type of disturbance.

EATING, SLEEPING, AND ELIMINATION PRACTICES OF A GROUP OF TWO-AND-ONE-HALF-YEAR-OLD CHILDREN

III. Sleeping Practices

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THE GUIDANCE given concerning sleep in the Well Child Clinic is similar to that given for eating, so far as general principles are concerned. Patterns of sleep at each age are discussed, changes are predicted, and mothers are helped to understand the individuality of the child's needs for sleep. Thus, as is true in other phases of development, mothers are helped to understand the child's progress, the primary purpose being to prevent serious problems from arising.

This study of sleep is based on information given by mothers during an interview; actual times of going to bed and getting up were not checked by a trained observer, just as in the study on eating, amounts of food eaten were not measured. Data were obtained on amount of sleep, sleeping arrangements, bedtime routines, and types of problems.

Table 1 gives the data on the total amount of sleep.

TABLE 1.—*Total Amount of Sleep in Twenty-Four Hours*

Number of Hours of Sleep in 24 Hr.	Children	
	No.	%
9 or less	1	0.2
10	7	1.0
11	50	7.3
12	171	25.0
13	293	42.8
14	130	19.0
15	25	3.7
16 or more	7	1.0
Total	684	100.0
Not stated	99	

Since no significant sex differences were observed, the data for boys and girls are presented in combined form. The total number of hours slept in 24 hr. varied from eight to 17, the average being 12.9, in close agreement with the average reported by Despert.[1] Total hours of sleep, of course, include both nap and night sleep. Almost all the children (95.5%) took naps (regularly, 83.5%; irregularly,

From the Rochester Child Health Institute. (The Rochester Child Health Institute was disestablished on July 1, 1951.)

1. Despert, J. L.: Sleep in Pre-School Children: A Preliminary Study, Nerv. Child **8**:8-27 (Jan.) 1949.

12%). The average length of the nap was 1.7 hr. About 90% of the children slept from one to three hours, the other 10% sleeping from three to five hours. Night sleep averaged 11.2 hr., the range being from less than eight to 14 or more.

These data merely confirm the principle of variability in all phases of development. Just as children vary in the amount of food they eat, so they vary in the number of hours they sleep. How widely can a child deviate from the average in his sleep pattern and function satisfactorily? Further study is needed on the children who make up the extreme groups. Why does one child need nine hours and another 16? Should these extremes be of concern to the pediatrician? What are the significant factors contributing to variability?

It is considered desirable by many people that each child sleep in a room alone, and many pediatricians encourage parents to have their children out of the parents' bedroom by 1 yr. at the latest. In Rochester only 27% of these children aged 2½ yr. slept in a room alone. About 29% slept in the room with parents, and the other 44% shared the room with siblings or other adults. It is true, however, that a very high percentage (95%) slept in a crib (75%) or bed alone (20%) even though they shared the room. Half of the 40 children (5%) who shared a bed did so with one or both parents.

There is psychiatric evidence that sleeping in the parents' bedroom may be a contributing factor to neurotic personality development. It will be interesting to follow the 220 children in this study who were still sleeping in the parents' bedroom at the age of 2½ yr., to see how many will manifest neurotic symptoms at a later age.

Almost everyone who has studied sleep in young children has observed that routines at bedtime are of importance to young children (Despert,[1] Spock,[2] Gesell and Ilg,[3] for example). Slightly more than 90% of this unselected group of children had definite enough routines that their mothers could describe them. About two-thirds of the routines were simple, the child asking for a drink, a kiss, and a special toy or blanket. About a third of the routines were elaborate and ritualistic. One child, for example, whose ritual required at least a half hour, always lay in her mother's bed after her shower with a towel around her, said her prayers, looked at three pictures on the wall, insisted that her three dolls be in their special places, and finally got into her own bed alone and asked for her washcloth, which she then sucked.

The great majority of children used some kind of comfort device as part of their routine, some having one or many toys, some wanting a bottle, others holding a special blanket. One little boy always took a beloved light cord to bed with him. About three-fourths of the children needed such objects for bedtime comfort. About half of the children used some form of self-comfort such as thumbsucking, hair twisting, rocking, and earpulling. Of course, some children used many comfort devices, some only one, and some none that were observable. No sex differences were found in the types of routines or comfort technics.

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2. Spock, B.: The Common Sense Book of Baby and Child Care, New York, Duell, Sloan & Pearce, Inc., 1946, pp. 258-259.

3. Gesell, A.; Ilg, F.; Learned, J., and Ames, L. B.: Infant and Child in the Culture of Today: The Guidance of Development in Home and Nursery School, New York, Harper & Brothers, 1943, p. 182.

About two-thirds of the mothers in this study said that their children usually slept through the night. The other third reported some interruption of sleep. The data are presented in Table 2.

The 63 children classed as wakeful were those who awakened during the night but did not cry or seemed to have bad dreams, or be in any way upset. The disturbed group were those who cried out, had night terrors or bad dreams, or talked in their sleep. It will be noted in comparing this group with those in Table 3 that not all children who had disturbed sleep were considered to present problems. Eleven of the children whose sleep was interrupted had night feedings. Of the 47 children who got out of bed during the night, 36 did so to get into the parents' bed, the other 11 to wander around, to go to the toilet, or to get a drink. The 36 children who got into the parents' bed were the same children shown in Table 3 as presenting problems.

TABLE 2.—*Frequency of Children with Spontaneously Interrupted Sleep*

Description of Child's Behavior	Children	
	No.	%*
Wakeful	63	8.1
Disturbed	230	29.6
Gets up	11	1.4
Gets into parents' bed	36	4.6

* The same child may be counted in more than one of these categories. The total number of children with interrupted sleep is 297. The percentages are based on a total group of 777 children.

TABLE 3.—*Frequency of Children with Various Types of Bedtime and Sleep Problems*

Description of Problem	Children	
	No.	%*
Resistance to nap	16	2.0
Resistance to going to bed	95	12.1
Resistance to going to sleep	4	0.5
Night terrors, bad dreams, and so forth	67	8.6
Gets into parents' bed	36	4.6

* The same child may be counted in more than one of these categories. The total number of children with problems is 166. The percentages are based on the total group of 783 children.

It is difficult to organize into a systematic framework the manifold varieties of conflict pertaining to sleep, and it is recognized that not all the problems included in Table 3 are of the same degree of seriousness. The problems are classified according to the overt difficulty, but the underlying disturbance seems to be the same, anxiety in the child or parent. Data on the types of sleep problems are given in Table 3.

Of the total group of 783 children, 21.2% were found to have one or more of these five bedtime or sleep problems. Some of these problems were of obvious concern to the mothers, especially those in which the mother and child were having constant conflict about bedtime. Some of the problems, however, were more subtle in nature, and their significance was not always consciously recognized by the mothers.

The most frequent problem was resistance to going to bed, 12.1% of the children in the total group being in this category. This group does not include those

children who did a legitimate amount of stalling, whose mothers accepted this pattern for a reasonable length of time and then exerted their rights as parents to call a halt firmly to the stalling, a procedure which the child in turn accepted. The problem type of resistance was made up of some or all of the following: persistent demands on the part of the child, endless putting off of getting into bed, repeatedly getting out of bed, parental irritation, but ineffectual attempts to make the child comply with the parents' wishes, punishments of various kinds from vague threats to spankings, the end result often being open conflict.

Questioning parents about sleep and bedtime routines not only elicits valuable information about the child's development but also gives the parent a chance to express some of her feelings about the child and her satisfactions and difficulties with him. The reactions of both parents and children to bedtime and sleeping give considerable insight into the parent-child relationship. Some children whose relationship with their parents is poor feel apprehensive about separation. Children of this age have difficulty in distinguishing clearly between phantasy and reality, and some may be especially fearful of imaginary objects that inhabit the dark. Some parents are not clear about their own feelings toward their children, and they find it difficult or impossible to set limits. Such a lack of clarity contributes to the child's anxiety, which he shows by his refusal to be separated from the parent.

Spock [4] discussed this same type of problem in infants and stated that ". . . the crucial factor in the picture is the mother's basic uncertainty which makes it difficult for her to set sensible limits. . . ."

About 30% of the total group of children studied woke up, talked in their sleep, cried out, or dreamed, but only 8.6% of the total group showed this behavior to a serious enough degree to be considered problems. The seriousness of the problem was judged by the frequency, intensity, and content of the disturbance. One child, for example, had cried out every night since infancy and during the past year had gritted her teeth during sleep. She screamed, "No, Mommy, no." This child had an exceedingly hostile mother, and there was ample evidence that the child had been maltreated. Another child woke up crying, "Don't let Jerry get me." A third child was reported to dream frequently and to wake up each night crying something similar to "The wind's going to blow me away." These children were able to express their fears verbally, whereas others cried out or woke up frightened without being able to tell what was wrong.

A small percentage of children (4.6% of the total group) persistently woke up during the night, got out of their own beds, and got into the parents' bed. Many children experiment with the possibility of sleeping with the parents, but most assured parents will comfort the child if necessary and see to it that the child returns to his own bed. For the small group of children considered problems, the parents were unable to resist the child's demands and in some cases fostered the child's desire to share the parents' bed.

A very small number of children and their mothers (2.0% of total group) made naptime an issue. These few mothers felt that the child must have a nap at any cost and tried to make him sleep, and the child resisted. Napping, at this age, seemed to be an acceptable part of the routine, and little conflict was apparent in a great majority of the children.

4. Spock, B.: Chronic Resistance to Sleep in Infancy, Pediatrics **4**:89-93 (July) 1949.

There was great variation in the amount of time these children took to fall asleep, and in only four instances was the time extreme enough to be considered a problem.

Of interest for further study are two sleeping arrangements found in this group of children aged 2½ yr. Twenty children regularly slept in the parents' bed, and in four families the parents slept in separate bedrooms, the child being in the room with one of the parents. A follow-up study of these children should be made to clarify the relation between these factors and the soundness of personality structure.

SUMMARY

The 783 children in this study slept an average of 12.9 hr., the range being from eight to 17 hr.

Naps were taken by 95.5% of the children.

Almost all the children (95%) slept in a crib or bed alone.

About 29% of the children in this study slept in the room with the parents.

All but 10% had bedtime routines, these routines varying in degree of complexity. Most of the children used some kind of comfort device.

About two-thirds of the children slept through the night without spontaneous interruption of their sleep.

Bedtime or sleep problems were found in 21.2% of the total group.

EATING, SLEEPING, AND ELIMINATION PRACTICES OF A GROUP OF TWO-AND-ONE-HALF-YEAR OLD CHILDREN

IV. Elimination Practices: Bowel

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IN THE first few decades of this century the dominant doctrine about toilet training was that it should be started at an early age and should be carried on in a fairly rigid way. The conscientious mother was taught to believe that cleanliness and regularity were virtues to be had at all costs. Since the late thirties and early forties, when pediatricians became aware of psychiatric thought and the relation between early training and the development of personality was more fully recognized, the teaching of parents has gradually changed. Along with the idea of self-regulation of eating came the idea of self-regulation of elimination.

In the Well Child Clinic mothers are helped to understand the importance of watching for signs of readiness in a baby before any new task is undertaken. In the case of toilet training the mother is advised to wait until the baby can sit up well, has shown some regularity in bowel functioning, and can give some signal of his desire to eliminate. The emphasis is put on the child's readiness for control rather than on the value of cleanliness and precocity of achievement. Mothers are helped to understand that precocious bowel and bladder control is not necessarily a sign of intelligence in either mother or baby and that wholesome attitudes toward elimination are far more important than the age at which control is attained. The responses of the mothers to this advice vary, depending on their own feelings about elimination and cleanliness.

The mothers of the 783 children in the study were asked about the frequency and regularity of the child's bowel movements, the extent of his independence in caring for his toileting, the occurrence of constipation, and any difficulties in training for bowel control.

Data on the frequency of bowel movements are given in Table 1. Boys and girls are not reported separately, since no sex differences were found in the frequency of bowel movements.

If the first three percentages in Table 1 are added together, it will be seen that 88.8% of the mothers said that their children had from one to three bowel movements a day. Those having a variable pattern, in which the frequency of the child's bowel movements was unpredictable, made up 7.6% of the group. A small per-

From the Rochester Child Health Institute. (The Rochester Child Health Institute was disestablished July 1, 1951.)

centage (3.5%) were reported to have a bowel movement every other day, and only 1 child in the total group showed extreme infrequency, with a movement once every three or more days.

In this group of children aged 2½ yr. the majority had at least one bowel movement a day. It cannot be ascertained from the data at hand whether this was the child's natural rhythm or his response to the mother's teaching that it is desirable to perform according to this pattern.

Mothers were asked if their children had their bowel movements at about the same time each day or at irregular times. Table 2 presents the results. In 48.7% of the cases mothers reported that their children had their bowel movements at

TABLE 1.—*Frequency of Bowel Movements*

Frequency	Children		
	No.	%	
1 time daily	477	61.2	88.8
1 time, occasionally twice	137	17.6	
2 or 3 times daily	78	10.0	
Variable pattern	59	7.6	
Every other day	27	3.5	
Extremely infrequent	1	0.1	
Total	779	100.0	
Not stated	4		

TABLE 2.—*Regularity and Variability of Bowel Movements*

Regularity	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Regular	187	53.1	187	45.1	374	48.7
Irregular	146	41.5	215	51.8	361	47.1
Variable	19	5.4	13	3.1	32	4.2
Total	352	100.0	415	100.0	767	100.0
Not stated	8		8		16	

$\chi^2 = 9.22$ $n = 2$ $0.01 > p > 0.001$

about the same time each day, and 47.1% said that they could not predict when the bowel movements would occur. A small percentage of children (4.2%) were variable, meaning that one bowel movement was at a regular time and the additional ones at any time during the day. The pattern of bowel movements in boys differed from that of girls in that boys more frequently had their bowel movements at a regular time of day than did girls.

By the age of 2½ yr. 92.2% of the girls and 77.5% of the boys were taking the responsibility for going to the toilet for their bowel movements. Data on responsibility are given in Table 3. Mothers took the responsibility for 14.4% of the boys and 3.8% of the girls; 8.1% of the boys and 4.0% of the girls shared the responsibility with their mothers. These differences between boys and girls are statistically significant.

Many pediatricians and psychiatrists agree that soiling before the age of 2 yr. cannot be considered a problem, but by the age of 2½ to 3 yr. it may be a sign of

disturbance in the parent-child relationship. English and Pearson [1] wrote: ". . . In many cases of soiling there is definite evidence of lack of parental love for the child. The soiling becomes a method of attracting the parents' attention and of spiting them. Starting on such a basis the soiling itself continues the difficulty between the child and the parents and the conflict situation by its increasing intensity, keeps up the soiling."

The majority of the children in this study (88.1%) had by the age of 2½ yr. achieved sufficient bowel control to be reliable about using the toilet either on their own initiative or in response to their mother's reminder. Some of the children (11.9%) had not yet established this control. The data are presented in Table 4.

These 93 children who were considered to have a bowel-training problem were similar in that they refused to have their bowel movements in the appropriate place.

TABLE 3.—*Responsibility for Bowel Movements*

	Boys		Girls		Total	
Responsibility	No.	%	No.	%	No.	%
Child's	279	77.5	390	92.2	669	85.4
Mother's	52	14.4	16	3.8	68	8.7
Shared	29	8.1	17	4.0	46	5.9
Total	360	100.0	423	100.0	783	100.0

$\chi^2 = 35.83$ $n = 2$ $p < 0.001$

TABLE 4.—*Incidence of Bowel-Training Problems*

	Boys		Girls		Total	
Problem	No.	%	No.	%	No.	%
No	302	83.9	388	91.7	690	88.1
Yes	58	16.1	35	8.3	93	11.9
Total	360	100.0	423	100.0	783	100.0

$\chi^2 = 11.41$ $n = 1$ $p < 0.001$

The depth of the disturbance of which soiling is a symptom varied in these children; in some the basic conflict seemed to be mild, and the symptoms could be expected to clear up easily; in others the conflict was severe, and bowel control could be established only as the severity of the basic disturbance was lessened.

Just as there was variation in the severity of disturbance, there was variation in the pattern of expression. In this group of 93 children there were some who had never achieved control, while others reverted to soiling only when they were upset. Some soiled themselves persistently, others only once or twice a week. A child might be compliant about sitting on the toilet and then have his bowel movement in his pants or on the floor after he got up from the toilet. Another type of child dribbled throughout the day, rather than having one complete bowel movement.

Although there were a few mothers who intellectualized the situation and said they accepted the child's lack of conformity, this seemed a rationalization to disguise

1. English, O. S., and Pearson, G. H. J.: Common Neuroses of Children and Adults, New York, W. W. Norton & Company, Inc., 1937, pp. 116-117.

their real feelings. Most mothers were definitely annoyed with the child and did not hesitate to say so. Most of them had "tried everything" from praise for an occasional success to persistent punishment.

The figures in Table 4 indicate that there were significantly more bowel-training problems among boys than among girls. This finding corroborates the statement often made by mothers that they find their boys harder to train than their girls. This difference may be related to varying rates of maturation in boys and girls or to the varying relationships between boys and girls and their mothers.

Table 3 (discussed previously) indicated a statistically significant difference between boys and girls in the frequency with which they accepted responsibility for taking care of their own elimination needs. In Table 5 these data are presented separately for 690 children without bowel-training problems and the 93 with bowel-training problems.

TABLE 5.—*Responsibility for Bowel Movements in Children With and in Children Without Bowel-Training Problems*

Responsibility	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Children with Problems						
Child's	6	10.4	10	28.6	16	17.2
Mother's	34	58.6	13	37.1	47	50.5
Shared	18	31.0	12	34.3	30	32.3
Total	58	100.0	35	100.0	93	100.0
$\chi^2 = 6.29$		$n = 2$		$0.05 > p > 0.02$		
Children Without Problems						
Child's	273	90.4	380	97.9	653	94.6
Mother's	18	6.0	3	0.8	21	3.1
Shared	11	3.6	5	1.3	16	2.3
Total	302	100.0	388	100.0	690	100.0
$\chi^2 = 19.99$		$n = 2$		$p < 0.001$		

There was a tendency for mothers of children with bowel-training problems to take responsibility oftener for their boys than for their girls. Likewise, even in children whose bowel control was well established, mothers took the responsibility for boys more frequently than for girls. From these data no conclusions can be drawn as to a causal relation, but one wonders what factors are operating in making mothers more solicitous of their boys than of their girls.

No study of bowel training in young children from a psychologic point of view can fail to include the subject of constipation. In our culture constipation is a word bandied about by radio, newspaper, and magazine, and everybody has a theory about its cause and a favorite remedy for its cure. Many parents consider it their duty to be concerned about the condition of the child's bowel functioning. In this study the parent was asked if the child was constipated and, if so, what was done about it. The interviewer tried to make clear to the mother that the frequency of the movement should not be used as the criterion of constipation but rather the consistency of the stool. There is some indication that the mothers understood this point, since about 78% of the constipated children were reported by their mothers to have one or more bowel movements a day (Table 6). Table 7 gives the number and percentage of children whose mothers reported them to be constipated.

One-fifth (20.4%) of the children were reported by their mothers to be constipated. Whether this reported constipation was actual or fictional, the psychologic significance of the results lies in the fact that these mothers considered their children to be constipated and were thus focusing undue attention on the anal area.

There was a tendency for girls to be constipated more frequently than boys ($0.05 > p > 0.02$), a finding in keeping with Macfarlane's [2] study, in which girls from 21 to 60 mo. had a higher incidence of constipation than boys. It will be remembered from Table 4 that boys were more likely to have bowel-training problems than were girls. What is the psychologic significance of these sex differ-

TABLE 6.—*Comparative Frequency of Bowel Movements in Constipated and in Nonconstipated Children*

Frequency of Bowel Movements	Constipated Children		Nonconstipated Children	
	No.	%	No.	%
1 time daily	98	62.0	377	61.1
1 time, occasionally twice	17	10.8	120	19.4
2 or 3 times daily	9	5.7	67	10.9
Variable pattern	19	12.0	40	6.5
Every other day	14	8.9	13	2.1
Extreme infrequency	1	0.6	0	0.0
Total	158	100.0	617	100.0
Not stated	1		7	
$\chi^2 = 28.06$	$n = 4$		$p < 0.001$	

TABLE 7.—*Incidence of Constipation in Children as Reported by Their Mothers*

Constipation	Boys		Girls		Total	
	No.	%	No.	%	No.	%
No	297	83.2	323	76.5	620	79.6
Yes	60	16.8	99	23.5	159	20.4
Total	357	100.0	422	100.0	779	100.0
Not stated	3		1		4	
$\chi^2 = 5.21$		$n = 1$		$0.05 > p > 0.02$		

ences? Do boys show their resistance outwardly more than girls? Do girls early begin to be withholding with their mothers and show their resistance in more subtle ways than do boys? It would be interesting to see what the results would be if fathers were primarily responsible for toilet training.

Of the 159 children who were called constipated by their mothers, only 11 had bowel-training problems. There is very little overlapping, then, of the two types of difficulties.

Table 6 gives the comparative frequency of bowel movements for children reported to be constipated and those not constipated. It will be noted that there is a statistically significant difference between the two groups, but not uniformly

2. Macfarlane, J. W.: Studies in Child Guidance: I. Methodology of Data Collection and Organization, Society for Research in Child Development Monographs, National Research Council, 1938, vol. 3, no. 6, p. 78.

so in the various frequency categories. However, while 91.4% of the nonconstipated children had at least one bowel movement a day, only 78.5% of the constipated children had this frequency of bowel movements. There is, therefore, a tendency for less frequent bowel movements to occur among the constipated children than among the nonconstipated children. This is associated with a less regular pattern as to time of movement ($0.02 > p > 0.01$).

Records at the Well Child Clinic were available for 120 of these 159 so-called constipated children. These 120 records were consulted to see how many of these mothers had made previous complaints of constipation in their children and if any treatment had been suggested by physician or nurse. In 72 (60%) of this group of 120 cases no mention of constipation was made in the child's record. In 48 (40%) constipation was mentioned one or more times. Some kind of treatment, such as prune juice, liquid petrolatum, or molasses had been prescribed in most of these 48 cases.

Data are incomplete on the mothers' reported management of the child's constipation; the type of management was stated for 127 of the 159 cases. In 32 of the 159 cases of constipation the question was not asked the mother, and therefore no

TABLE 8.—*Mother's Management of Child's Constipation*

Mother's Management	Boys		Girls		Total	
	No.	%	No.	%	No.	%*
Diet	29	61.7	50	62.5	79	62.2
Laxative	12	25.5	16	20.0	28	22.1
Lubricant	8	17.0	9	11.2	17	13.4
Enema	5	10.6	6	7.5	11	8.7
Nothing specific	2	4.3	7	8.8	9	7.1
Suppository	3	6.4	2	2.5	5	3.9

* Percentages are based on 127 children (47 boys and 80 girls) for whom both constipation and its treatment are known and not on the total group of 783 children.

information was available. Of the 127 children (47 boys and 80 girls) for whom there were data, the mothers of all but nine (7.1% of this group) tried in some way to "treat" the constipation. The data are given in Table 8; since more than one kind of treatment can be used with each child, the total percentage of types of management is more than 100.

The most frequent single method of control of constipation by these 127 mothers was the use of fruit, vegetables, molasses, or some other food. This method is listed in the table as diet, 62.2% of these mothers using this type of management. About a fifth (22.1%) used some kind of laxative, many of them milk of magnesia. Lubricants were used by 13.4% of these 127 mothers. A smaller percentage reported the use of enemas (8.7%) or suppositories (3.9%).

How much constipation there is in the population at different ages is still largely a matter of conjecture. A true estimate of the frequency of constipation is difficult to make, since the drugstore is often a substitute for medical consultation for this widely advertised "complaint." The data presented in this study indicate that constipation may begin early in the life of the child and be fostered by the adult's preoccupation with it. Thus, any treatment of a child's constipation, if the constipation is primarily psychologic in origin, should include counseling for the mother, to enable her to lessen her own concern about elimination.

SUMMARY

Most (88.8%) of the 779 children in this part of the study had one or more bowel movements a day.

About half the children had their bowel movements at approximately the same time each day and the other half at an unpredictable time. Boys were significantly more "regular" than girls.

More girls than boys in this study took the responsibility for going to the toilet alone.

All but 11.9% of the children in this study had achieved satisfactory bowel control. More boys than girls had bowel-training problems.

One-fifth of these children aged 2½ yr. (20.4%) were reported by their mothers to be constipated. There was a tendency for more girls than boys to be constipated.

Mothers attempted to alleviate constipation by diet, laxatives, lubricants, enemas, and suppositories; all but 7.1% of the mothers in this part of the study used one or more of these methods of control.

In the 127 cases in which children had been reported by their mothers to be constipated at 2½ yr., 60% of the mothers had made no previous mention of this complaint at their visits to the Well Child Clinic. In the other 40% constipation had been mentioned one or more times, and some kind of treatment had been prescribed in most of these cases.

EATING, SLEEPING, AND ELIMINATION PRACTICES OF A GROUP OF TWO-AND-ONE-HALF-YEAR OLD CHILDREN

V. Elimination Practices: Bladder

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THE DEVELOPMENT of bowel control in young children and its relation to personality development has been more carefully studied by research workers and clinicians than has that of bladder control. Continuous studies of the same children are needed in order to understand the process by which children establish urinary control and its relation to personality structure. Interest has been focused on enuresis as a problem in older children,[1] and studies have been done in retrospect, but little documentation has been given on children in the process of becoming enuretic. Is it possible by studying children at the ages at which urinary control is being established to get clues for the prediction of later problem syndromes of which enuresis is a part?

Like all other aspects of growth, the development of urinary control is complex, and this study will contribute only a small part of the information that is needed to enable one to understand the developmental process. The intention is to present data on the status of 783 children aged 2½ yr. relative to urinary control as reported by their mothers. The study is primarily a statistical presentation and raises more questions than it answers. An intensive study of the dynamic aspects of the development of urinary control is needed to get at the underlying psychologic factors.

There is general agreement that the completion of urinary control usually comes later in the developmental cycle than does that of bowel control. In this aspect of development there are, of course, individual differences; some children attain bladder control before they do bowel control, while others develop control of both bowel and bladder functions at about the same time. Pearson,[2] in discussing the relation between bladder training and personality development in the child, said: "He needs an optimum period of gratification for his infantile sensual desires. It is generally agreed that it is best for the development of a child that . . . his daytime bladder training take from two and a half to three years, his nocturnal bladder training take from three to three and a half years. . . ."

From the Rochester Child Health Institute. (The Rochester Child Health Institute was disestablished on July 1, 1951.)

1. Gerard, M. W.: Enuresis: A Study in Etiology, Am. J. Orthopsychiat. **9**:48 (Jan.) 1939.

2. Pearson, G. H. J.: Emotional Disorders of Children: A Case Book of Child Psychiatry, New York, W. W. Norton & Company, Inc., 1949, p. 24.

In the Well Child Clinic mothers are helped to estimate their child's readiness for the development of urinary control and to understand the variability in the age at which control is established. Since urinary control appears to be more easily achieved in the third year of life if early pressure is avoided than if it is applied, mothers are advised to postpone a definite training program until near the beginning of the third year.

The children in this study are 2½ yr.; hence, lack of urinary control in itself should not be considered a sign of delayed development. Not enough is known about norms to determine what should be called a bladder-training problem at this age; therefore, in this section of the study there will be no enumeration of problems.

Even though the mothers of these children have been advised to be tolerant and leisurely about bladder training, there are some, of course, who for reasons of their own have been insistent and persistent in attempting to get results fast and early. Some children were "successfully trained" by 1 yr. and remained so; some were dry for a period and then regressed to wetting again after illness, holidays or moving, or out of resentment toward their mothers.

TABLE 1.—*Frequency of Daytime Urination*

	Boys		Girls		Total	
Frequency	No.	%	No.	%	No.	%
Frequent	29	8.1	45	10.7	74	9.5
Moderate	293	82.3	324	77.3	617	79.6
Infrequent	21	5.9	43	10.3	64	8.3
Variable	13	3.7	7	1.7	20	2.6
Total	356	100.0	419	100.0	775	100.0
Not stated	4		4		8	
$\chi^2 = 9.98$		$n = 3$		$0.02 > p > 0.01$		

In the interview mothers were asked about the child's frequency of urination, his willingness to assume responsibility for his toilet needs during the waking hours (hereafter referred to as the day or daytime), the progress being made in control during the day, at nap, and at night, and whether or not he was taken up at night.

Table 1 gives the data on frequency of urination during the day. "Frequent" means that the child urinated every hour or less; "moderate" means every two or three hours; "infrequent" means every four hours or more, and "variable" means an unpredictable pattern.

Approximately four-fifths of this group of children have a two-hour or three-hour interval for daytime urination. Smaller numbers (9.5% and 8.3%) are included in the frequent and infrequent categories. Twenty children (2.6%) are classified as having a variable pattern.

The distribution of the frequency of urination of the boys tends to be different from that of the girls ($0.02 > p > 0.01$), a smaller proportion of boys than of girls being reported by their mothers to urinate infrequently.

Table 2 presents the data on whether the mother or the child takes the responsibility for daytime urinary control. At the age of 2½ yr. 91.4% of the 418 girls and 78.8% of the 358 boys were responsible during the major part of the time for making known their need to urinate. Mothers assumed the responsibility for reminding the child to go to the toilet four times as often for boys as for girls

(11.7% as compared with 2.9%). Likewise, in those instances in which responsibility was shared between mother and child, the frequency was greater among the boys than among the girls (9.5% as compared with 5.7%). These differences between boys and girls in the taking of responsibility are statistically significant. These findings on the taking of responsibility for urinary needs parallel those for bowel movements. Since mothers seem to be more solicitous of their boys than of their girls, one wonders if it is because boys actually need more help than girls or if there is a psychologic factor operating that encourages mothers to keep their boys more dependent on them. Perhaps mothers let girls at this age take more initiative than boys in managing their toileting needs. Perhaps girls are more compliant with their mothers than are boys, or it may be that mothers are more fastidious about girls and help them to be clean earlier than boys, so that by the age of 30 mo. girls are further advanced than are boys.

Since mothers were not regularly asked whether their boys urinated standing up or sitting down at this age, a statistical presentation of the data cannot be made. Further study should be done on this aspect of development, for in some cases, at

TABLE 2.—*Responsibility for Daytime Urinary Control*

	Boys		Girls		Total	
Responsibility	No.	%	No.	%	No.	%
Child's	282	78.8	382	91.4	664	85.6
Mother's	42	11.7	12	2.9	54	6.9
Shared	34	9.5	24	5.7	58	7.5
Total	358	100.0	418	100.0	776	100.0
Not stated	2		5		7	

$\chi^2 = 28.92$ $n = 2$ $p < 0.001$

least, there was a suggestion that the boy who was still urinating sitting down tended to be an emotionally immature child. These boys should be studied to determine whether they will be in the group who later have trouble in making a satisfactory masculine identification.

Each mother was questioned about her child's progress in keeping dry during the day, during nap, and at night. If the child was wet at any time, the mother was asked how frequently and under what conditions. She was also questioned about her nighttime procedures of taking the child up, of letting him call, or of letting him sleep through the night. If the child wet himself oftener than twice a month in one of the three periods, he was considered to be wet at some time in a given period. The results on the incidence of dryness and wetness for day, nap, and night are given in Table 3.

Approximately the same percentage of children were dry in the day as were dry at night (59.9% and 56.6% respectively). The observed frequency of daytime wetting (40.1%) is not in agreement with Gesell and Ilg's [3] statement about children 2½ yr. that "there are very few daytime accidents." During the nap, 84.1% were dry and 15.9% were wet. In each of these three periods more boys than girls were

3. Gesell, A.; Ilg, F. L.; Learned, J., and Ames, L. B.: Infant and Child in the Culture of Today: The Guidance of Development in Home and Nursery School, New York, Harper & Brothers, 1943, pp. 185-186.

wet, the differences being statistically significant. This finding is in keeping with the remark often made by mothers that boys are harder to train than girls.

In the previous section it was stated that more boys than girls had bowel-training problems. Although incomplete urinary control is not considered a problem at the age of 2½ yr., the persistent difference between boys and girls in the estab-

TABLE 3.—*Incidence of Dryness and Wetness*

Condition	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Day						
Dry	183	50.8	286	67.6	469	59.9
Wet	177	49.2	137	32.4	314	40.1
Total	360	100.0	423	100.0	783	100.0
$\chi^2 = 22.77$		$n = 1$		$p < 0.001$		
Night						
Dry	173	48.1	270	63.8	443	56.6
Wet	187	51.9	153	36.2	340	43.4
Total	360	100.0	423	100.0	783	100.0
$\chi^2 = 19.78$		$n = 1$		$p < 0.001$		
Nap						
Dry	254	78.9	339	88.5	593	84.1
Wet	68	21.1	44	11.5	112	15.9
Total	322	100.0	383	100.0	705	100.0
Not stated	38		40		78	
$\chi^2 = 12.15$		$n = 1$		$p < 0.001$		

TABLE 4.—*Frequency of Lack of Urinary Control During the Day, Night, and Nap*

Periods When Wetting Occurs	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Day only	52	16.2	59	15.4	111	15.8
Night only	48	14.9	55	14.3	103	14.6
Day and night	50	15.5	39	10.2	89	12.6
Day, nap and night	53	16.4	25	6.5	78	11.1
Night and nap	15	4.7	17	4.4	32	4.5
Day and nap	0	0.0	1	0.3	1	0.1
Nap only	0	0.0	1	0.3	1	0.1
Total wet at some time	218	67.7	197	51.4	415	58.8
Total dry all the time	104	32.3	186	48.6	290	41.2
Total number of cases on which percentages are based	322	100.0	383	100.0	705	100.0
Not stated	38		40		78	

lishment of bladder control raises the same questions as were asked about bowel control. Is the difference related to varying rates of maturation in boys and girls, to differences in biological organization, or does the difference lie in the varying relationships between boys and girls and their mothers? Undoubtedly both inherited and training factors are involved in the development of bladder control.

Data on urinary control during the day and night and at nap were complete on 705 of the 783 children. Table 4 gives the number and percentage of children who were wet during certain periods and those who were dry all the time.

The table shows that 58.8% of these 705 children aged 2½ yr. were wet at some period of the day or night and 41.2% were reliably dry all the time. Children at this age are in the process of achieving urinary control, and these figures indicate that fewer children were reliably dry all the time than were wet at some period of the day or night.

Among the 415 children who were wet at some time, about the same percentage were wet only in the day as were wet only at night. The children who were wet only in the daytime were dry at night, and those who were wet only at night were dry in the day. Some children were wet both day and night but were dry at nap. Others were wet in the day, at nap, and at night. One child was wet only at nap, and one, during the day and at nap. Those in the remaining group were wet at night and at nap. Thus, while there was considerable variation in the patterns of achieving urinary control, the data indicate that the majority of children achieved control during naptime first; thus, 73.0% of those who were wet at sometime were dry at naptime, or, stated differently, only 15.8% of the 705 children were wet at naptime.

TABLE 5.—*Frequency of Daytime Urination of Children Who Are Dry All the Time and of Those Who Are Wet at Certain Times**

Frequency of Daytime Urination	Dry All the Time		Wet in Day Only		Wet at Night Only		Wet at Nap and Night		Wet Day and Night		Wet Day, Nap and Night	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Frequent	20	7.0	10	9.0	3	2.9	3	9.4	12	13.8	14	18.2
Moderate	229	79.8	89	80.2	89	86.4	28	87.5	70	80.5	56	72.7
Infrequent	36	12.5	8	7.2	10	9.7	1	3.1	1	1.1	1	1.3
Variable	2	0.7	4	3.6	1	1.0	0	0.0	4	4.6	6	7.8
Total	287	100.0	111	100.0	103	100.0	32	100.0	87	100.0	77	100.0
Not stated	3		0		0		0		2		1	

* The groups wet at nap only and wet day and nap are not included in this table as there is only one case in each group.

It would take a more detailed study than this one to get at the reasons in different children for lack of bladder control during the day and night. But there is evidence in the reports given by these mothers that some children wet themselves when they were mad at their mothers, some when they were outdoors playing, some when the new baby arrived, others following hospitalization. In this study no account has been taken of the possible effects of seasonal variations on day and night wetting.

It has already been stated that in this study more boys than girls were wetting themselves at the age of 2½ yr. Table 4 shows that 16.4% of the boys were wet during the three periods, day, night, and nap, whereas only 6.5% of the girls were in this category, a difference which is statistically significant ($p < 0.001$).

The children included in Table 4 can be grouped in a progressive series from dry all the time to wet at one, two, or three periods: dry all the time, 41.2%; wet at one period, 30.5%; wet at two periods, 17.2%; wet at three periods, 11.1%. These data seem to indicate that the majority of children do not suddenly become reliably dry. Rather, the acquisition of bladder control is a gradual process. These groups need to be studied independently, however, for more information is needed on the order in which children attain urinary control.

Table 5 gives the frequency of daytime urination for the children who were consistently dry and those who were wet at certain times. The question is often

asked about the relation between the child's frequency of urination and his stage of urinary control. In other words, if he is dry all the time, does he urinate less often than if he is wet during the three indicated periods? This table shows that 72.7 to 87.5% of the children fell in the group who had a moderate interval of urination (every two or three hours) regardless of their wetness or dryness. The children designated as wet day and night or wet day, nap, and night show a shift in the direction of greater frequency of urination, 13.8 and 18.2% being in the group of frequent urination and 1.1 and 1.3% being in the infrequent group.

While frequency of urination may be associated with the child's ability to keep dry, it is evidently not the most significant factor. Thus, of the 62 children who urinated frequently, 32% were dry all the time, as contrasted with the 42% who were dry in the remainder of the group. The fact does remain, however, that if a child urinated at infrequent intervals, he was likelier to be dry than wet.

One of the most persistent questions parents ask physicians about the development of urinary control in young children is whether or not to take the child up at night. The parents want to know if taking the child up facilitates his having a dry

TABLE 6.—*Responsibility for Nighttime Control as Reported by Mothers*

	Boys		Girls		Total	
Responsibility	No.	%	No.	%	No.	%
Taken up by parent	73	20.6	85	20.3	158	20.4
Child calls parent	66	18.6	76	18.1	142	18.4
Child gets up alone	5	1.4	9	2.2	14	1.8
Child not taken up	210	59.4	249	59.4	459	59.4
Total	354	100.0	419	100.0	773	100.0
Not stated	6		4		10	

bed. There is a considerable variety of opinion. Gesell and Ilg [3] stated that "picking up is more palliative at this age than instructive. . . . The majority, however, need to be picked up and even then may still be wet in the morning." [3] Spock [4] said, "Staying dry at night is another thing that the bladder learns itself. . . . In other words, the bladder sometimes 'trains' itself before anybody has a chance to train it."

Some physicians say that it makes no difference and that the child's stage of development is the crucial factor; when the child is ready to be dry at night, he will be dry, regardless of whether he is taken up or allowed to sleep through the night. Other physicians advocate taking the child up at regular times during the night; this group believes that the child who is taken up will achieve nighttime control sooner than the child who is not taken up. If the child is resistant to being picked up at night, some physicians will advise that the mother let him alone until he is more accepting of this procedure.

Table 6 gives the figures on responsibility for nighttime urinary control as reported by 773 mothers of children aged 2½ yr. One-fifth (20.4%) of the children were taken up by the mothers at least once during the night, while three-fifths (59.4%) were not taken up. In 18.4% of the cases the child called the parent to make known his toileting needs, and in 1.8% of the cases the child got up alone.

4. Spock, B.: The Common Sense Book of Baby and Child Care, New York, Duell, Sloan & Pearce, Inc., 1946, p. 201.

It can be seen from this table that about three times as many children were *not* taken up as *were* taken up during the night to urinate. There are no significant sex differences in any of the figures presented in Table 6.

In Table 7 data are presented for the children who were dry during the night and those who were wet during the night in relation to whether they were taken up by the parent, called the parent, got up alone, or slept through the night. Girls who were dry during the night are distributed in the four categories of responsibility in approximately the same percentages as girls who were wet. Boys, however, show a difference. The percentages of the first two categories (taken up by parent and

TABLE 7.—*Relation of Nighttime Urinary Control to Responsibility*

Responsibility	Boys		Girls		Total	
	No.	%	No.	%	No.	%
Children Dry During the Night						
Taken up by parent	20	11.7	49	18.3	69	15.7
Child calls parent	49	28.7	48	17.9	97	22.1
Child gets up alone	5	2.9	8	3.0	13	3.0
Not taken up by parent	97	56.7	163	60.8	260	59.2
Total	171	100.0	268	100.0	439	100.0
Not stated	2		2		4	
Children Wet During the Night						
Taken up by parent	53	29.0	36	23.8	89	26.6
Child calls parent	17	9.3	28	18.6	45	13.5
Child gets up alone	0	0.0	1	0.7	1	0.3
Not taken up by parent	113	61.7	86	56.9	199	59.6
Total	183	100.0	151	100.0	334	100.0
Not stated	4		2		6	
χ^2 based on totals = 26.44			$n = 3$		$p < 0.001$	

TABLE 8.—*Relation of Nighttime Urinary Control to Responsibility*

Responsibility	Dry		Wet		Total
	No.	%	No.	%	No.
Taken up by parent	69	43.7	89	56.3	158
Child calls parent	97	68.3	45	31.7	142
Not taken up	260	56.6	199	43.4	459
Total	426	56.1	333	43.9	759

child called parent) among boys who were dry are different from the corresponding percentages among boys who were wet. In other words, 11.7% of the boys who were dry were taken up by their parents, as compared with 29.0% of the boys who were wet, and 28.7% of the boys who were dry called their parents to make known their toileting needs, while only 9.3% of the boys who were wet called their parents.

Analysis based on the totals for both sexes in Table 7 indicates that the distribution of the two groups (dry versus wet) among the enumerated categories of responsibility is significantly different. A larger proportion of the children who were wet than of the children who remained dry were taken up by their parents, while the reverse was true of those who called their parents. Approximately the same percentage of children who were dry and of those who were wet during the night were not taken up by their parents to urinate, about 59% of each group.

By rearranging the data of Table 7 in Table 8, evidence may be obtained concerning the possible effectiveness of the parents' taking the child up during the night for the purpose of keeping him dry. The figure of 43.7% may be taken as a measure of the maximal (and possibly exaggerated) estimate of the effectiveness of taking children aged 2½ yr. up during the night to keep them dry. This value is to be contrasted with the 56.6% of those not taken up who were dry and the 68.3% who called their parents and who were dry. It seems valid to conclude that the taking up of these children aged 2½ yr. during the night was only a moderately successful procedure in keeping them dry.

The real motivation underlying the taking of responsibility for nighttime urinary control is not definitely known in these cases, but the question can be raised as to the significance of the relationship between children and their parents in the development of urinary control. It looks as if boys and girls are responding urethrally in a different fashion, depending on whether the parent or the child is taking the initiative. For example, 73% of the boys who were taken up by the parents were wet, while only 26% of the boys who called the parents were wet. The figures for the girls are not so clear-cut. Whereas a definite majority of boys who were taken up by the parent were wet, girls who were taken up showed much smaller differences between wetness and dryness (58% dry versus 42% wet). Both girls and boys who called the parent tended to be dry, the percentages being 63 and 74 respectively. Thus, when the responsibility was the parent's, boys were likely to be wet and girls tended to be dry. When the responsibility was the child's, a high percentage of both boys and girls were dry, but there was a higher percentage of dry boys than girls. It may be that girls at the age of 2½ yr. are making a greater effort to be compliant with the parent than are boys, or the difference may lie in the relationships between mothers and their boy and girl children as they work together in the establishment of control.

As was mentioned previously, no specific problems in bladder training will be discussed in this study, since the purpose has been to find out the status of children at the age of 2½ yr. in the achievement of urinary control. With these data now available, a further study needs to be done on what deviations are significant. There is evidence (not presented here) that some children are expressing anxiety through the urinary function. Mothers and children are often in conflict in this area as well as in the others already discussed. Some mothers, in their zeal to have a child who meets their own standards and what they think are cultural expectations for toilet training, become punitive and increase the child's need to rebel against this type of authority by active or passive resistance. Some children lose their urinary control under the varying stresses of their lives.

Any developmental process leading to control is a significant one to study, for it throws light on the way in which control becomes integrated into the personality structure. Buxbaum [5] has discussed the relation between bladder control and character formation in children:

> The way they control their body establishes the pattern of their general self-control. If unable to control their body, they are also unable to control their feelings. They cannot wait; every whim has to be fulfilled immediately. They become furious and helpless when they are crossed, bursting out in temper tantrums which overwhelm them, like the stream of urine overwhelms

5. Buxbaum, E.: Your Child Makes Sense: A Guidebook for Parents, New York, International Universities Press, Inc., 1949, pp. 119-120.

their body. . . . Some children are difficult to manage, others are completely ruled and dominated by their mothers, are timid and lacking of initiative. The conviction that the child is unable to control his body gives him a feeling of being unable to achieve anything and he feels discouraged in trying anything new.

Are those children who at 2½ yr. have made little progress in bladder control (wet day, nap, and night) the ones who later will show poor self-control, who are easily frustrated, whose drive is poor, who are fearful, or who have difficulty in adjusting to authority?

Are the children who are wet only in the day different from those who are wet only at night? What is the significance of the choice of period when a child wets himself? Which children are most likely to regress at a later age? Which children are later enuretic? Which children make steady progress toward good control and have no difficulty in the urinary function? In other words, barring organic defect, which patterns of wetting at this age are predictive of later disturbances?

SUMMARY

Approximately four-fifths of the children in this study had a two-hour or three-hour interval for daytime urination.

In 85.6% of the cases the child, rather than the mother, took the initiative for his own daytime toileting needs, girls taking the initiative oftener than boys.

Approximately the same percentage of these children were dry in the day (59.9%) as were dry at night (56.6%).

Most of the children (84.1%) were dry at nap.

More girls than boys were dry in all three periods, day, nap, and night.

Fewer children were reliably dry all the time (41.2%) than were wet at some period of the day or night (58.8%).

Three-fifths of these children aged 2½ yr. were not taken up by their parents during the night to urinate. One-fifth were taken up. One-fifth either called the parent or got up alone.

A larger proportion of the children who were wet than of those who were dry were taken up by the parent during the night to urinate. Approximately the same percentage of children who were dry and of those who were wet during the night were not taken up (about 59% of each group). More dry than wet children called the parent during the night to make known their toileting needs.

Taking these children up during the night was only a moderately successful procedure in keeping them dry. Of the children taken up by the parent, 43.7% were dry, as contrasted with 56.6% of those not taken up and 68.3% of those who called their parents.

IDIOPATHIC FAMILIAL HYPERLIPEMIA

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IDIOPATHIC familial hyperlipemia is a rare disorder. Hyperlipemia associated with certain known pathologic conditions is not uncommon; it may be found in cases of diabetes mellitus, certain diseases of the kidney, liver and pancreas, hypothyroidism, starvation, anemia, occlusive vascular disease, certain dermatoses, glycogenosis (von Gierke's disease) and Niemann-Pick disease. Only seven cases of idiopathic hyperlipemia in children are found in the literature,[1] with an equal number in adults being reported.[2] Bürger and Grütz[1a] (1932) described the first case, of an 11 year old boy with hyperlipemia, hepatosplenomegaly and a nodular xanthomatous skin eruption which appeared and disappeared with rise and fall of the blood lipid level. Opitz[1b] (1935) described a 12 year old boy with hyperlipemia and splenomegaly but without xanthomatous skin eruption. Franklin[1c] (1937) reported a case of a 5 year old girl who had no skin lesions but had splenomegaly and hyperlipemia. Bernstein[1d] (1939) reported a 6 year old boy with hyperlipemia, hepatosplenomegaly, xanthomatous skin lesions and a history of recurrent abdominal pain. Holt[1e] (1939) reported a detailed study of an 11 year old girl with hepatosplenomegaly, hyperlipemia, lipemia retinalis, skin lesions and abdominal crises. The mother, aged 39, and a sister, aged 15, had hyperlipemia; while a brother, aged 8, had hepatosplenomegaly in addition to hyperlipemia. Good-

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1. (*a*) Bürger, M., and Grütz, O.: Über hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut, Arch. Dermat. u. Syph. **166**:542, 1932. (*b*) Opitz, H.: Hochgradige Lipämie unklarer Genese bei einem 12 järhigen Knaben, Deutsche med. Wchnschr. **61**:89 (Jan. 18) 1935. (*c*) Franklin, S. M.: Splenomegaly with Lipemia, Proc. Roy. Soc. Med. **30**:711, 1937. (*d*) Bernstein, S. S., and others: Metabolic Observations on Child with Essential Hyperlipemia, J. Pediat. **14**:570 (May) 1939. (*e*) Holt, L. E., Jr., Aylward, F. X., and Timbres, H. G.: Idiopathic Familial Lipemia, Bull. Johns Hopkins Hosp. **64**:279 (May) 1939. (*f*) Goodman, M.; Shuman, H., and Goodman, S.: Idiopathic Lipemia with Secondary Xanthomatosis, Hepatosplenomegaly and Lipemia Retinalis, J. Pediat. **16**:596 (May) 1940. (*g*) Levey, B. M.: Idiopathic Lipemia, ibid. **29**:367 (Sept.) 1946.

2. (*a*) Grossman, E. E., and Hitz, J. B.: Lipemia Retinalis Associated with Essential Hyperlipemia, Arch. Ophth. **5**:570 (Nov.) 1948. (*b*) Shore, S. C., and Schrire, V.: A Possible Case of Idiopathic Hyperlipemia, Clin. Proc. **6**:138, 1947. (*c*) Bloomfield, A. L., and Shenson, B.: The Syndrome of Idiopathic Hyperlipemia with Crises of Violent Abdominal Pain, Stanford M. Bull. **5**:185, 1947. (*d*) Thannhauser, S. J.: Lipidosis: Diseases of the Cellular Lipid Metabolism, ed. 1, New York, Oxford University Press, 1940, p. 181; ed. 2, 1950, pp. 263; 278-281.

man [1f] (1940) reported a patient, aged 1, in whom the xanthomatous skin lesions disappeared with a low fat diet; no lipase could be demonstrated in the blood, and examination of other members of the family revealed no hyperlipemia. Levey [1g] (1946) described an 8 year old child with hepatosplenomegaly, lipemia retinalis, abdominal pain and a milky serum with cholesterol slightly increased; no determination of blood neutral fats was done.

Because of the rarity of this condition and of certain additional features we have had the opportunity to observe, the present case report seems justified.

REPORT OF CASE

First Admission.—A 2 year old boy was presented in the outpatient clinic Jan. 10, 1950, with a complaint of "hives and nosebleeds"; he was admitted to the hospital for study because enlarged spleen and liver were found on physical examination.

The family history revealed the father, aged 27, to be living and well, although he complained at times of "sinus trouble" and had a tendency to bruise easily. The mother, aged 23, had

Fasting Blood Lipid Determinations Under Various Conditions for the Patient and Other Members of His Family

	Total Lipids, Mg./100 Cc.*	Phospholipid Phosphorus, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	
			Total	Esters
Patient				
1st admission, 1/13	2,925	70.4	320	188
Ward diet, 1/16	2,100	14.6	290	169
Low fat diet, 2/7	1,688	15.85	287	206
2d admission, 4/3	6,680	12.1	...	...
Fat-free diet, 4/17	1,206	4.83	...	...
3d admission, 5/15	2,700	16.95	286.5	123.5
Mother	1,632	38.8	158	120
	1,240	11.43	...	...
Sibling	1,032	14.15	...	...
	900	16.85	190	149.7
Maternal aunt	825	12.3	135	102.3
Maternal grandmother	1,588	15.25	...	...

* Normal, 500 to 750 mg. per 100 cc.

"hives" as a child but considered herself a healthy adult. The patient was the result of her first pregnancy; in the second there was miscarriage of an undetermined cause at four months, and she was eight months pregnant at the time of admission of the patient. There was no history of tuberculosis, diabetes, specific allergies or known familial diseases.

The patient was the result of a normal full term pregnancy and suffered no difficulty during the newborn period. He was breast-fed for three months and was then placed on an evaporated milk formula because the mother produced insufficient milk to satisfy him. He was started on soft foods at four months, and all foods were added rapidly to his diet. When egg was added, he broke out in "fine red bumps," and its use was discontinued. Feeding of orange juice at 2 months was also followed by a similar skin rash. With these two exceptions, he had a full diet, taken from the family table, since 1 year of age. He sat alone at 3 months, cut his first tooth at 5 months, stood alone at 8 months, walked at 1 year and talked at 1½ years. He had had no immunizations and no specific diseases.

The mother had thought of him as a fairly healthy boy until two months prior to admission, when she noted red spots appearing on his legs in crops that enlarged with vesicle formation and after a few days spontaneously drained a substance resembling milk, after which the lesion would gradually dry and leave a bluish discoloration which appeared to itch. After the first two weeks or so the lesions no longer ruptured and drained but appeared as hives over the entire body and subsided within an hour or so, leaving a discoloration like that of old bruises. The mother could not think of any condition which seemed to influence the appearance

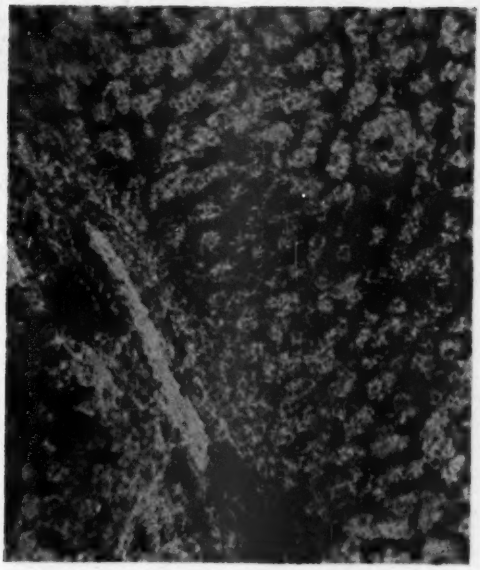

Fig. 1 (AMH-8291-L).—First liver biopsy on ward diet, showing excessive fat accumulated in liver. Low power (× 270); sudan II.

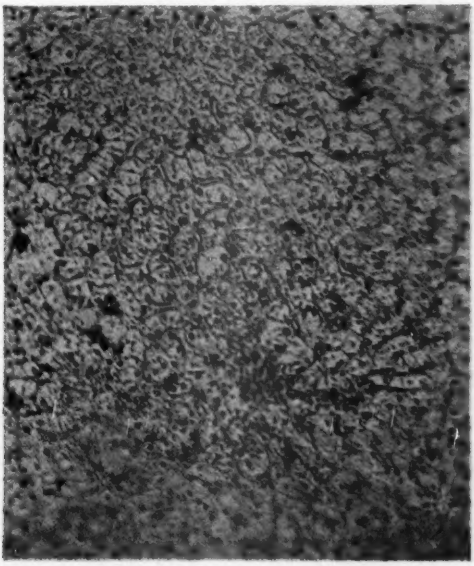

Fig. 2 (AMH-8291-Q).—Marked reduction of fat in liver biopsy specimen after one week on fat-free diet. Low power (× 270); sudan II.

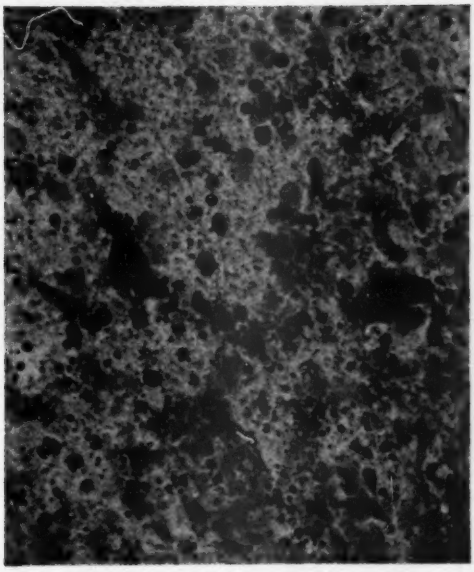

Fig. 3 (AMH-8291-K).—First liver biopsy on ward diet, showing excessive fat accumulated in liver cells. High power (× 540); sudan II (oil red O).

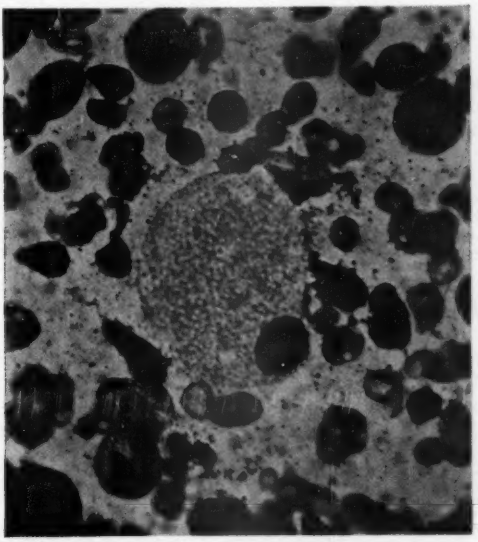

Fig 4 (AMH-8291-G).—Bone marrow smear, showing large macrophage filled with fat. High power (× 540).

and disappearance of these lesions. There were no accompanying systemic symptoms. For several months the child had had mild nosebleeds each time he had a cold. The mother felt that his abdomen had always been somewhat large and that for the past six months it had appeared more prominent. There were no other symptoms revealed in a general review of the major systems.

On physical examination he appeared to be a normally nourished, normally developed 2 year old boy, weighing 29 pounds (13 Kg.), in no acute distress but rather quiet, with a prominent abdomen and a pallor of his palms, lips and scleras. There were several discolored areas resembling old bruises on both thighs. On each arm and in the right axilla were found several small papules containing yellowish material with a dry scaly surface. Lymph nodes were palpable in all areas but were small and not tender. Except for the marked pallor of the mucous membranes, the ears, nose and mouth appeared normal. The eyes appeared normal, but on funduscopic examination the vessels appeared as white channels and veins could not be distinguished from arteries. The fundi generally were pale in appearance and thought consistent with lipemia retinalis. The lungs were normal. There was a rather harsh systolic murmur to the left of the sternum at the third intercostal space, without other abnormal heart findings.

On the first drawing of blood for laboratory studies the clue to the nature of his difficulty was disclosed when the serum appeared as milk. The following are the results of laboratory studies. The white blood cell count was 9,000, with 50 per cent neutrophils, 48 per cent lymphocytes and 2 per cent monocytes. The red blood cell count was 4,700,000; hemoglobin level, 12.6 Gm. per 100 cc.; bleeding time, 1 minute 45 seconds, and coagulation time, 3 minutes 4 seconds. There was no sickling. The fragility test gave normal results, and prothrombin time was 14 seconds. The urine gave negative reactions for sugar and albumin; the specific gravity was 1.025, and a microscopic examination showed no abnormalities. Blood urea nitrogen level was 13.7 mg. per 100 cc.; blood sugar, 117 mg.; serum chlorides as sodium chloride, 560 mg.; nonprotein nitrogen, 30.2 mg.; cholesterol, 320 mg.; cholesterol esters, 188 mg., or 54 per cent, and carbon dioxide, 46.2 volumes per cent. The cephalin flocculation reaction was 2+; amylase activity, 65 Somogyi units. Stools showed no ova or parasites; the dry feces fat content was 29.1 Gm. per 100 Gm.; the blood lipid level was 2,295 mg. per 100 cc. (table). The turbidity of the serum made the results of the thymol turbidity test and the total serum protein determination and the albumin-globulin ratio very inaccurate, and they are, therefore, not reported.

Roentgenograms of the lungs and heart showed them to be normal. Skeletal survey revealed no deviation of bone from normal. Electrocardiography gave normal results.

Bone marrow examination showed that there was a definite increase in the lymphocytes. Cells not usually present in marrow were seen. These were large mononuclear cells varying in size, 10 to 40 times that of a red cell. They were filled with fat droplets and represented macrophages filled with fat (fig. 4).

Needle biopsy of the liver revealed that the liver cells showed a good deal of vacuolization, and these vacuoles had a granular appearance. The tissue was otherwise normal. There was no inflammation. The fat stain demonstrated that the many vacuoles were filled with fat. It was not felt that there was fatty metamorphosis or degeneration but that this condition might be described as lipid storage (figs. 1 and 3).

With the above findings there seemed no doubt that we were dealing with a case of idiopathic hyperlipemia. The patient was placed on a low fat diet of an intake of approximately 15 Gm. fat daily. At the end of one week another blood lipid determination showed that there was a reduction from 2,100 to 1,688 mg. per 100 ml. of blood. His xanthomatous lesions had disappeared, his spleen and liver were somewhat smaller, and he was discharged on February 7, to be followed in the outpatient clinic while he continued on a low fat diet.

Second Admission.—The patient remained well, active and happy at home until April 2, 1950, when he became feverish and listless. He was brought to the clinic on April 3 and was admitted for further study. His febrile episode cleared up rapidly without there being other symptoms or signs to permit a specific diagnosis. On physical examination, there were no xanthomatous skin lesions, the spleen was 3 fingerbreadths below the costal margin and the liver was 1 fingerbreadth below the costal margin. Additional laboratory figures were blood lipase,

0.68 unit (normal, 0.2 unit); stool fat, 18.2 Gm. per 100 Gm. of dry feces. The epinephrine tolerance test showed a fasting sugar level of 112 mg. per 100 cc., and after one hour a level of 160 mg.

He was then placed on a diet without fat for one week, at the end of which time blood lipid determination, bone marrow examination and liver biopsy were repeated. Blood lipids were reported as 1,206 mg. per 100 ml. The bone marrow was identical with that of the previous examination, with the exception that the large cells filled with fat were few and were found with difficulty. The liver biopsy showed the following. The lobular architecture was preserved. The cell cords were well formed, and there was no increase in fibrous tissue about the portal areas. No inflammatory infiltrate was noted. The polygonal cells were very finely vacuolated. Sections stained for fat revealed numerous tiny stainable granules within the parenchymal cells.

Fig. 5 (April 5).—Normal nutrition and enlarged spleen and liver at second admission.

Large fat vacuoles were demonstrated within liver cells. Globules of stainable material approximately twice the size of an erythrocyte were present within the sinusoids and also seemed to occur within certain of the Kupffer cells. By comparison with sections of the material obtained at the previous liver biopsy, it appeared that there was almost no fat present in the liver at the time. Very small amounts did persist, however, and as in the previous biopsy, it appeared that most of the stainable fat was in relation to the reticuloendothelial cells of the sinusoids rather than to the liver cells themselves.

At this time he seemed more agile and playful in the ward; his mucous membranes were pink; his retinal vessels could be distinguished, and the spleen had receded to 1 to 2 finger-breadths below the costal margin. The patient was discharged April 22, with specific instructions to the mother for a very low fat diet.

Third Admission.—He continued well until during the noon meal on May 12, 1950, when he complained of abdominal pain. He finished his meal but during the afternoon complained frequently of pain in his abdomen, which appeared to occur or increase in paroxysms. The pain was of such severity as to cause him to cry out. No vomiting, diarrhea, or other symptoms were noticed by the mother. She claimed to have adhered to the low fat diet, and the only indiscretion known to her was his exposure to a box of cream chocolates the previous day, of which he ate an undetermined amount. By evening the abdominal pain, which seemed to be to the left of the umbilicus, had become so severe that he was taken to another hospital; the admission diagnosis was an acute condition within the abdomen. Report from that hospital was to the effect that exploration for possible intussusception was being contemplated when the mother gave the additional history that we had been following the patient. A telephone call to us resulted in his transfer. On admission he was in no apparent acute distress; his temperature was 101 F. rectally, and he appeared somewhat somnolent. The skin was clear, and there was no adenopathy. Mucous membranes of nose and pharynx were hyperemic, and there were rhonchi in both lung fields. The abdomen was slightly protuberant, with the liver 2 fingerbreadths and the spleen 4 fingerbreadths below the costal margin. There were generalized resistance to palpation and some apparent tenderness on palpation of the spleen; however, no masses or other enlarged viscera were palpated. Rectal examination showed no abnormalities. A roentgenogram of the chest and a flat film of the abdomen showed no abnormalities. The white blood cell count was 19,000, with 54 per cent neutrophils and 46 per cent lymphocytes. The urine was normal. It was felt that he had a mild respiratory infection and that his abdominal pain represented an abdominal crisis as reported in idiopathic hyperlipemia. Comparison of the size of his liver and spleen at this time with that at the time of his second discharge showed that there had been a definite increase in the size of these organs, which was more marked in the spleen. It was therefore decided that surgery was not indicated.

Within 24 hours after admission he appeared much brighter, became afebrile, ate normally and was without evidence of discomfort. During the next five days of his hospitalization the size of the spleen was observed to decrease. He was discharged May 18 on a low fat diet, to be followed at frequent intervals in the outpatient clinic.

An attempt was then made to demonstrate the familial character of this disorder by determination of blood fat in other members of the family. As shown in the table, the mother and maternal grandmother appeared to have a significant increase in their fasting blood lipid levels, while the sibling and a maternal aunt did not appear to have a significant increase. The father was not available for study. No associated or contributing condition was found on examination of the mother and grandmother.

COMMENT

The diagnosis of idiopathic familial hyperlipemia is not difficult and is one of exclusion after the clue of "milky serum" is recognized at the time of taking blood. Glycogenosis and Niemann-Pick disease are easily excluded by the familiar clinical picture of these conditions. Other conditions sometimes associated with hyperlipemia, mentioned earlier, are likewise ruled out with little difficulty by history and common laboratory determinations. According to Thannhauser,[3] it should be emphasized that the main distinguishing feature in idiopathic hyperlipemia from a laboratory standpoint is the high level of neutral fat in the serum, this increase being five to 40 times the normal, while the cholesterol and phospholipids are only secondarily increased two to five times the normal values.

There are two types of skin lesions reported for idiopathic familial hyperlipemia, both of which have been present in our patient. The eruptive form of xanthoma was found in four of the cases reported (Bürger and Grütz,[1a] Bernstein,[1d] Holt [1e] and Goodman [1f]). These yellowish-colored, discrete papules appear and disappear with the increasing and decreasing hyperlipemia. Bürger and Grütz [1a] examined by

3. Thannhauser, S. J.: Personal communication to the authors.

biopsy one of these papules and reported that it did not show true xanthomatous tissue but only a few scattered foam cells. The second type of lesion has been described only in Holt's [1e] case and appeared to occur chiefly during the summer months which corresponds with the history of our patient, in whom (prior to admission) vesicular lesions developed which spontaneously discharged a "milky fluid." Thannhauser [3] believes that in reality there is only one type of xanthomatous lesion but that it may appear in one of two phases, the vesicular phase progressing to the fully developed xanthomatous phase or regressing and disappearing after the vesicle opens.

Lipemia retinalis appears to be a fairly constant finding and is recognized by the creamy color of the retinal vessels. The vessels on emerging from the nerve head are pink-cream color, becoming pure cream-colored at the periphery. It is impossible to distinguish arteries and veins because of the color. With the rise and fall of the blood fat, this distinctive feature in color can be observed to change concurrently.

Attacks of abdominal pain have been described in four of the seven cases (Opitz,[1b] Holt,[1e] Goodman [1f] and Levey [1g]). As in our case, these attacks may simulate an acute condition within the abdomen, which will result in surgical exploration unless the true nature of the condition is recognized. A rapid enlargement of the spleen and liver was noticed in Holt's [1e] case, with abdominal pain, and this enlargement would seem to be the causative mechanism for pain. It would seem clear that the enlargement of the liver is due to fat deposit by the apparently large amount of fat demonstrated in our case by liver biopsy and the markedly reduced amount following a fat-free diet, with reduction in the size of the liver (fig. 4). Postmortem observations on organs have been described by Thannhauser [2d] and Chapman [4] on Goodman's [1f] patient only, who died of an intercurrent disease. The possibility of the intercurrent disease in this case having changed the fat content in these organs must be considered, since an almost total lack of histologic evidence of abnormal fat deposit in the organs or in the reticuloendothelial system was reported. Neither were there any other findings to explain the abdominal crises in this case.

The familial characteristic of the disease has apparently not been looked for in all cases reported but was found only in the case of Holt.[1e] Our case (table) appears to demonstrate the trait on the maternal side in the mother and grandmother, with a sibling showing no evidence of the condition.

The deficiency responsible for this abnormal metabolism of fat remains obscure. In the case of Goodman [1f] no lipase was found in the blood, though other enzymes were present. It was thus postulated that if the amount of lipase in the blood is an index of the concentration and activity of this enzyme in the tissues, the failure of fat deposition could be accounted for by lack of the necessary enzymes in the tissues. Blood lipase has not been determined in all cases reported; however, Bloomfield [2c] reported normal values in his patient, and our patient showed an adequate amount of this enzyme in the blood.

Thannhauser [2d] suggested that the condition is dependent on failure of fat deposition and storage, that the patient receives no more fat in his diet than a normal

4. Chapman, F. D., and Kinney, T. D.: Hyperlipemia: "Idiopathic Lipemia," Am. J. Dis. Child. **62**:1014 (Nov.) 1941.

person but is unable to deposit it normally in fat depots. Consequently, fat accumulates in the blood and in the reticuloendothelial elements of the body. More recent experiments of Thannhauser and Stanley,[5] in which iodine^{131}-labeled neutral fat was administered orally to normal subjects and to those with idiopathic hyperlipemia, support Thannhauser's suggestion, since they showed that the disappearance of iodine from the blood serum was considerably prolonged in the latter as compared with the normal subjects. At present a hypothesis of Thannhauser,[2d] which indicates that a functional disorder of the capillaries causes a retention of neutral fat in idiopathic hyperlipemia, is the most acceptable explanation for the condition.

The prognosis as to life in cases of idiopathic hyperlipemia would appear to be good, since the only necropsy report concerns the case of Goodman,[1f] and this patient died apparently for reasons other than those directly associated with the hyperlipemia.

The level of blood lipids has been repeatedly reported to rise and fall with changes in the amount of fat ingested, with corresponding improvement in the condition of the patient with a low fat intake. We have been able to control our patient during hospitalization by a low fat diet, and it is strongly suspected that lack of control in his home environment is due to indiscretions. Other than a diet low in fat, there remains no specific treatment.

SUMMARY

Idiopathic familial hyperlipemia is a rare disorder, with only seven cases in children and an equal number in adults being found in the literature.

A case is presented which has been found to have all the classic findings associated with the condition: hepatosplenomegaly, xanthoma of the skin, lipemia retinalis, high blood neutral fat level with only slightly elevated phospholipids and cholesterols, absence of other pathologic conditions producing hyperlipemia, abdominal crises, decrease in blood fat on a low fat diet and the demonstration of hyperlipemia in other members of his family.

Four color prints show a fat-laden macrophage from bone marrow and specimens from liver biopsies done before and after treatment with a fat-free diet. It is believed that the large amount of fat in the liver, as demonstrated by biopsy, is the cause of the visceral enlargement and that rapid accumulation of fat in the abdominal viscera could well explain the abdominal crises frequently observed in this condition.

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5. Thannhauser, S. J., and Stanley, M. M.: Serum Fat Curves Following Oral Administration of I^{131}-Labeled Neutral Fat to Normal Subjects and Those with Idiopathic Hyperlipemia, Tr. A. Am. Physicians **62**:245, 1949.

EPIDEMIC POLIOMYELITIS

Review of Five Hundred Twenty-Six Cases

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POLIOMYELITIS was an epidemic disease throughout the country in 1949. In New York during the last half of the year 526 patients were observed and treated in the Willard Parker Hospital. These cases do not represent a true cross section of the epidemic as it occurred in the city (2,446 cases reported [1]), but rather a concentration of the more severely involved patients. The purpose of this paper is to present briefly some of the clinical and pathological aspects of these cases, noting certain symptoms referable to the gastrointestinal tract. Reference will also be made to therapeutic procedures and the use of certain drugs. Several of these subjects will be presented in more detail in future reports.

TABLE 1.—*Classification of Cases*

Type	Cases	Deaths	Case Fatality Rate, %
Nonparalytic	141	0	0.0
Paralytic	...	..	...
Spinal	256	1	0.3
Bulbar	42	10	23.8
Bulbar-spinal	61	20	32.8
Bulbar-encephalitic	6	3	50.0
Bulbar-spinal-encephalitic	17	6	35.3
Spinal-encephalitic	3	0	0.0
Total	526	40	7.6

CLASSIFICATION OF CASES

Cases were classified as either nonparalytic or paralytic, with the pure type and combinations of spinal, bulbar, and encephalitic types fitting into the latter group (Table 1). There were 141 (26.8%) nonparalytic and 385 (73.2%) paralytic cases. Bulbar involvement occurred in 126 cases (23.9%). Diagnosis was based on the history and the physical findings, with spinal fluid changes as supportive evidence. Data on the abortive form of poliomyelitis are not included in these statistics, since a definite diagnosis of poliomyelitis is usually not possible.

From the Poliomyelitis Service, Willard Parker Hospital.

1. Greenberg, M.; Siegel, M., and Magee, M. C.: Poliomyelitis in New York City, 1949, New York J. Med. **50**:1119 (May 1) 1950.

HISTORY

In common the history was that of a general systemic infection characterized by upper respiratory, digestive, and meningeal irritative manifestations. Symptoms followed a progressive clinical course with or without the development of muscle weakness. The biphasic "dromedary" course was less often noted. In one patient, a 5½-yr.-old boy, symptoms of bulbar poliomyelitis developed 10 days after tonsillectomy and adenoidectomy, and he died of progressive bulbar poliomyelitis four days after admission.

PHYSICAL FINDINGS

The common physical findings were an elevated temperature, injected pharynx, and stiffness of the neck, back, and hamstring muscle groups in varying degrees of prominence. Reflex changes during the acute illness varied from normal to hyperactive and then to diminished or absent when muscle weakness developed. The Kernig, Brudzinski, and "tripod position" signs were usually positive. Spinal fluid cell counts averaged 142 per cu. mm., ranging from 0 to 1,539, with usually an increase in the total protein content. There were 22 patients (4.1%) with no changes in the spinal fluid. Muscle weakness developed in 10 of these, and in the remaining 12 muscle tightness was a prominent symptom for several days.

AGE AND SEX INCIDENCE

The average age was 9.5 yr., with a range from 6 mo. to 42 yr. There was a slight predominance of male patients. The greatest number of cases occurred in the group 5 to 14 yr. of age; in the group over 14 there were 99 cases (18.8%). Multiple cases, all of the paralytic type, occurred in 10 families. Of the 41 female patients 18 yr. or over, for six (14.5%), all paralytic, the poliomyelitis was complicated by pregnancy.

MORTALITY

In this series there were 40 deaths (7.6%); in 39 cases there had been bulbar involvement, and in these death was attributed to failure of the vital centers. In the other case, of a respirator patient with severely involved spinal poliomyelitis, death was due to mechanical failure of the respirator. In 33 patients (82.5%) there were symptoms of complete failure of the circulatory center. In these patients there were a rapid, often irregular pulse, a falling blood pressure, and finally signs of terminal shock, with a cold, clammy, mottled cyanotic skin, confusion, coma, and an inaudible heart beat before respirations ceased.

Hyperthermia occurred in six of the fatal cases. In spite of standard corrective procedures, temperatures rose to heights that could not be recorded on the average clinical thermometer (over 108 F.).

PATHOLOGY

At autopsy pathological lesions such as described by others [2] were demonstrated in the brain, brain stem centers, and spinal cord. Lesions were present in the

2. (*a*) Smith, L. W., cited in Poliomyelitis, International Committee for the Study of Infantile Paralysis, Baltimore, Williams & Wilkins Company, 1932, p. 295. (*b*) Landon, J. F., and Smith, L. W.: Poliomyelitis: A Handbook for Physicians and Medical Students, New York, The Macmillan Company, 1934, pp. 28 and 30. (*c*) Bodian, D.: Poliomyelitis: Neuropathologic Observations in Relation to Motor Symptoms, J. A. M. A. **134**:1148 (Aug. 2) 1947.

central nervous system more extensively than clinical signs indicated. The lungs showed evidence of edema, congestion, bronchopneumonia, and in some instances interstitial pneumonia such as observed by Saphir.[3] There was evidence of focal atelectasis, but there were no patients with massive atelectasis. Focal myocarditis, as noted by Dolgopol and Cragan[4] was found in one-quarter of the cases.

The pathological features demonstrated in the stomach were edema and marked congestion of the capillary bed, perivascular extravasation of blood, and focal erosion of gastric mucosa, with evidence of blood in the gastric cavity. Congestion of Peyer's patches of the ileum was also frequently noted. In one case there was a perforation of the fundus of the stomach explained as a postmortem autolysis and perforation.

GASTROINTESTINAL SYMPTOMS

Vomiting of coffee-ground material occurred in 16 (12.7%) of the bulbar poliomyelitis cases, and 11 (68.7%) of the patients died. In some patients there were tarry stools, and anemia was noted on blood examination. This type of vomiting was considered an unfavorable prognostic sign and usually appeared within 24 hr. preceding death. In one case, however, of a 14-yr.-old boy with bulbospinal poliomyelitis, a respirator patient with marked encephalitic symptoms, vomiting of coffee-ground material occurred over a period of several days prior to death. A postmortem perforation of the fundus of the stomach was noted at autopsy.

In some instances the vomiting of coffee-ground material was thought to be due to bleeding from the passage of stomach tubes or from the use of nasal catheters for oxygen administration and nasopharyngeal suction. In most cases, however, gastric tubes were not passed, and oxygen was administered by a two-holed metal nasal clip rather than by catheter, and no bleeding was noted to be due to nasopharyngeal suction. It was felt that the coffee-ground vomitus in most instances was a reflection of the gastrointestinal lesions.

Although no true peptic ulceration was found in those cases in which autopsy was done, the characteristic gastrointestinal pathological changes were found present in more or less severity. Smith in 1931 [2a] and Landon and Smith in 1934 [2b] reported congestion of the stomach mucosa and submucous hemorrhage in nearly 75% of the poliomyelitis cases in which autopsy was done; in some cases there was surface erosion of the mucosa. They attributed these lesions to viral action.

Reports of cases of peptic ulceration in this disease have appeared in the literature. Heyde and Robinson[5] reported the clinical and pathological findings of two such bulbar poliomyelitis cases. One patient, a 4½-yr.-old girl, had vomited chocolate-colored material before death, and postmortem examination revealed a perforation of the fundus of the stomach. More recently, two fatal cases of perforation of esophageal ulcers in bulbar poliomyelitis in adults were reported.[6]

3. Saphir, O.: Visceral Lesions in Poliomyelitis, Am. J. Path. **21**:99 (Jan.) 1945.

4. Dolgopol, V. B., and Cragan, M. D.: Myocardial Changes in Poliomyelitis, Arch. Path. **46**:202 (Aug.) 1948.

5. Heyde, E. C., and Robinson, S.: Acute Peptic Ulceration Accompanying Bulbar Poliomyelitis: Report of 2 Cases, Gastroenterology **11**:519 (Oct.) 1948.

6. Erskine, F. A.; Mason, J. H., Jr., and McDade, H.: Perforation of Esophageal Ulcers in Bulbar Poliomyelitis: Report of 2 Cases, Am. J. Med. **8**:239 (Feb.) 1950.

In view of the gastrointestinal lesions that are demonstrated in fatal cases of poliomyelitis and in view of the reports of gastric, duodenal, and esophageal ulceration and perforation accompanying bulbar poliomyelitis, the various hypotheses proposed regarding the causation of acute gastrointestinal ulceration suggest themselves for brief review. These include (*a*) the neurogenic theory: gastric hemorrhage and acute ulceration have been described in association with brain tumors and as following injuries and operations on the brain,[7] and experimental ulcers have been produced in animals by the production of lesions in the brain stem [8] and by prolonged stimulation of the vagus [9]; ulcers frequently occur in nervous persons and in those under emotional tension [10]; (*b*) the acid-peptic theory: the influence of the acid factor and the decrease in the protective properties of the mucosa may cause ulceration; however, small acute and subacute gastric ulcers may occur in the absence or diminution of the secretion of acid [11]; (*c*) the vascular theory: circulatory insufficiency and ischemia of the gastric wall, possibly on a basis of vasomotor disturbances,[12] may be causative factors; more recently [13] angiospasm has been emphasized; (*d*) miscellaneous theories: other factors such as trauma, infection, allergy, and endocrine disturbances have been suggested; (*e*) the theory of the general adaptation syndrome [14]: reactions following continued exposure to stress and the breakdown of the hormonal adaptation mechanism manifest themselves, among other conditions, in gastrointestinal ulcers, observed with shock, burns, and intense emotional excitement.

Some of these mechanisms are present to a greater or lesser degree in acute bulbar poliomyelitis and may contribute to the development of the severe gastrointestinal lesions.

GENERAL TREATMENT

The general medical and nursing management was similar to that used for any acute febrile disease. Communicable disease technic was employed until 48 hr. following the febrile period. Patients were handled as little as possible early in the disease, and effort was made to relieve the apprehension of the patient and to gain his cooperation. Sedative drugs were usually avoided, since they mask symp-

7. Cushing, H.: Peptic Ulcers and the Interbrain, Surg., Gynec. & Obst. **55**:1 (Jan.) 1932.

8. Fulton, J. E.: Physiology of the Nervous System, London, Oxford University Press, 1938, p. 253.

9. Manning, G. W.; Hall, G. E., and Banting, F. F.: Vagus Stimulation and the Production of Myocardial Damage, Canad. M. A. J. **37**:314 (Oct.) 1937.

10. Mittelman, B., and Wolff, H. G.: Emotions and Gastroduodenal Function, Psychosom. Med. **4**:5 (Jan.) 1942. Wolf, S., and Wolff, H. G.: Evidence on the Genesis of Peptic Ulcer in Man, J. A. M. A. **120**:670 (Oct. 31) 1942.

11. Palmer, W. L., and Nutter, P. B.: Peptic Ulcer and Achlorhydria: A Further Study of the Role of Acid Gastric Juice in Pathogenesis of Peptic Ulcer, Arch. Int. Med. **65**:499 (March) 1940.

12. Boles, R. S.; Riggs, H. E., and Griffiths, J. O.: The Role of the Circulation in the Production of Peptic Ulcer, Am. J. Digest. Dis. **6**:632 (Nov.) 1939.

13. Smith, E.; Rosenblatt, P., and Limauro, A. B.: The Role of the Sympathetic Nervous System in Acute Poliomyelitis, J. Pediat. **34**:1 (Jan.) 1949.

14. Selye, H.: The General Adaptation Syndrome and the Disease of Adaptation, J. Clin. Endocrinol. **6**:117 (Feb.) 1946.

toms of hypoxia and encephalitis and contribute to respiratory difficulty. Patients with the bulbar type of disease and those with respiratory difficulty were under continuous observation.

Urinary retention was often encountered in patients with spinal involvement. Some patients were given furfrethonium (furmethide® iodide)[15] intramuscularly, with satisfactory results in most instances.

PAIN AND MUSCLE TIGHTNESS

With the exception of a few patients, notably adults, muscle pain was not a predominating feature in this series. It may be that the early institution of moist heat served to minimize this complaint.

Relief of muscle tightness and pain was accomplished satisfactorily by the application of hot packs—the "lay-on" type applied to the patient in the prone position and occasionally the Kenny "wrap-around" packs. Warm baths were used early for small children.

An attempt was made to evaluate clinically certain drugs that have been advocated for the relief of muscle spasm and pain. Priscoline® (2 benzyl-2-imidazoline hydrochloride),[16] a sympathicolytic drug, was administered orally to 68 patients in the dosage used and recommended by Smith.[17] It was our feeling that most of the patients were not benefited by its use. It did have a relaxing and analgesic effect in some patients, but this was not consistent or sustained, and when administration of the drug was stopped, tightness recurred. In other patients it was thought that the muscle tightness was increased by the drug, and the return to hot packing gave quick relief. There were uncomfortable side effects such as nausea and vomiting, and since the drug must be continued for long periods, its potentiality for more serious reaction was always present. In general, our physical therapy staff preferred the hot packs, and we had sufficient personnel to carry out such procedures.

Diethylaminoethanol hydrochloride,[18] a procaine derivative, was administered by vein to 10 patients. Its relaxing and analgesic effects were of a temporary nature and not very effective or satisfactory for our use.

EXPERIMENTS IN SPECIFIC TREATMENT

The possibility that the lesions of poliomyelitis may be on the basis of an allergic reaction and might therefore respond to the antihistaminic drugs was suggested to us by Volterra.[19] A group of 10 patients, with nonparalytic and early spinal paralytic disease, were given chlorprophenpyridamine (chlor-trimeton®) maleate,[20] an antihistaminic agent, in doses of 2 to 4 mg. every four hours orally for 48 hr. It was our impression that the drug had no therapeutic value in this disease. However, this subject may merit further investigation.

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15. Lawson, R. B., and Garvey, F. K.: Paralysis of the Bladder in Poliomyelitis, J. A. M. A. **135**:93 (Sept. 13) 1947.

16. Supplied by Ciba Pharmaceutical Products, Inc., Lafayette Park, Summit, N. J.

17. Smith, E.; Graubard, D. J.; Goldstein, N., and Bikoff, W.: A New Method in the Management of Acute Anterior Poliomyelitis, New York J. Med. **48**:2608 (Dec.) 1948.

18. Winthrop-Stearns, Inc., 170 Varick St., New York.

19. Volterra, M.: Personal communication to the authors.

20. Supplied by Schering Corporation, 2 Broad St., Bloomfield, N. J.

Aureomycin in large doses was given to 38 controlled patients with nonparalytic poliomyelitis without effect on the clinical course of the disease.[21]

An automatic refrigerating unit, manufactured by the Thermo-O-Rite Products Company, Buffalo, employed in refrigeration anesthesia,[22] was used to prevent the extreme fever which may occur in some poliomyelitis patients. It was also used in an attempt to decrease viral activity in the spinal cord by bringing the spinal fluid temperature below body temperature.[23] This was tried in 18 patients, and the impression was that the apparatus produced an antipyretic effect but did not alter the course of the disease.

BULBAR AND ENCEPHALITIC MANAGEMENT

There were 126 patients (23.9%) with bulbar involvement[24] (Table 2). Diagnosis was based on evidence of involvement of the lower four cranial nerves. Other cranial nerve palsies were present in some instances and also involvements of the vital centers—respiratory and vasomotor. The common early symptoms were nasal voice, difficulty in swallowing, loss of the gag reflex, and pharyngeal accumulation of mucus. To avoid the dangers of aspiration of pooled secretions and regurgitated food and fluids, postural drainage was instituted immediately on admission, the foot of the bed or respirator being elevated 30 degrees above the horizontal. Pharyngeal suction was done only when necessary, care being taken to avoid trauma. Fluids were given parenterally during the febrile period, and overhydration was avoided. Nasal gavage was instituted cautiously, and later when the patient was able to swallow his saliva, small amounts of clear fluids were given by mouth. Oxygen was given by nasal catheter or by a two-holed metal clip, which was placed just inside the external nares. Pulmonic infection was prevented by frequent change of position and by the use of antibiotics. Drugs to dry up secretions, such as atropine, were not used.

TABLE 2.—*Cases with Bulbar Involvement*

Type	Cases	Deaths	Case Fatality Rate, %	Tracheotomy		
				Cases	Deaths	Case Fatality Rate, %
Bulbar	42	10	23.8	2	2	100.0
Bulbar-spinal	61	20	32.8	3	3	100.0
Bulbar-encephalitic	6	3	50.0	0	0	0.0
Bulbar-spinal-encephalitic	17	6	35.3	1	1	100.0
Total	126	39	30.9	6	6	100.0

Tracheotomy was performed on six patients when other treatment failed to maintain an adequate airway and when hypoxia seemed to be progressing. These

21. Appelbaum, E., and Saigh, R.: Aureomycin in the Treatment of Poliomyelitis, J. A. M. A. **143**:538 (June 10) 1950.

22. Crossman, L. W.; Allen, F. M.; Hurley, V.; Ruggiero, W. F., and Warden, C. E.: Refrigeration Anesthesia, Current Res. in Anesth. & Analg. **21**:241 (Sept.-Oct.) 1942.

23. Allen, F. M.; Safford, F. K., Jr., and Wheeler, W. L., Jr.: Unpublished data.

24. Lenarsky, M.: Bulbar Poliomyelitis, Arch. Pediat. **67**:250 (June) 1950.

patients had profuse secretions, uncontrollable by continuous suction. Although there was immediate improvement in three patients, all six died.

There were 26 patients with encephalitic involvement. These patients showed varying degrees of disorientation, confusion, drowsiness, and coma. These symptoms persisted despite intensive oxygen therapy, with oximetric readings indicating adequate oxygenation. Two patients remained comatose for 14 days. A transitory change in the intellect was observed in several patients.

Involvements of the vital centers in poliomyelitis are serious and are responsible for almost all the deaths from this disease. Two drugs were used as central stimulants, with success in some instances. Caffeine and sodium benzoate was used for central respiratory depression and phenylephrine (neo-synephrine®) hydrochloride 1% for failure of the vasomotor center.[25]

Dysfunction of the respiratory center was indicated by irregularities of rate, rhythm, and depth of respiration. Caffeine and sodium benzoate in repeated doses of 0.25 to 0.5 gm. for children and adults respectively was administered intramuscularly. Some patients were maintained on a four-hour schedule. A good response, noted in most cases within minutes, was indicated by more regular respiration and better air exchange. The respirator was necessary for some patients. The availability of the respirator for respiratory difficulty due to peripheral or central failure, and in addition the use of central stimulation for the latter, minimized fatality from these causes.

Dysfunction of the vasomotor center did not respond so well to central stimulation. Phenylephrine 1% was administered in repeated doses of 2.5 to 5.0 mg. for children and adults respectively, intramuscularly and in some instances intravenously by slow drip. Several patients responded temporarily, and three patients with very marked symptoms eventually recovered. However, indicative of the severity of the involvement of the vasomotor center is the fact that 33 of the deaths (82.5%) were attributed to failure of this center.

USE OF THE RESPIRATOR

The respirator had its prime use in the respiratory difficulty due to involvement of the muscles of respiration, the intercostals and the diaphragm, and treatment was most successful in such cases. Patients were put into the respirator before exhaustion ensued, and whenever possible attempts were made to gain their cooperation by explanation of the purpose and value of the procedure. Negative pressure rarely exceeded 14 cm. of water, and positive pressure up to 5 cm. was used in some instances. Fourteen patients with spinal involvement were treated in the respirator. All recovered but one, who died because of mechanical failure of the apparatus.

The respirator is not so effective when there is bulbar involvement, although with severe central respiratory depression, it can be of help. When the bulbar poliomyelitis patient has involvement of the respiratory muscles, the respirator may be necessary. Adequate management of the bulbar disease eliminates the complications that can occur for bulbar poliomyelitis patients in the respirator and obviates in most instances the need for tracheotomy. Frequent change of position, prophy-

25. Stimson, P. M.: The Diagnosis and Treatment of Bulbar Poliomyelitis, South. M. J. 42:415 (May) 1949.

lactic antibiotic therapy, and use of oxygen were routine measures. Forty-one (74.5%) of the respirator patients had bulbar involvement, and 13 (31.7%) recovered (Table 3).

To avoid overdependence on the respirator, weaning was started early, even the first day when possible. By this means patients were encouraged to assist more actively toward recovery. The rocking bed [26] was an asset in the weaning procedure. With this apparatus, too, objections and apprehension had to be overcome and relieved before patients appreciated its value. Motion sickness was not a significant feature.

Studies of vital air capacity of the lungs [27] were made, and it was found that patients were able to remain out of the respirator for long periods with vital capacities as low as 15% of the estimated normal and became completely independent with a vital capacity as low as 18%.

TRANSPORTATION FATIGUE

The importance of early bed rest and the avoidance of fatigue as therapeutic and preventive measures in poliomyelitis have been stressed. Russel [28] has shown

TABLE 3.—*Respirator Cases*

Type	Cases	Deaths	Case Fatality Rate, %	Tracheotomy		
				Cases	Deaths	Case Fatality Rate, %
Spinal	14	1	7.1	0	0	0.0
Bulbar	7	6	85.7	2	2	100.0
Bulbar-spinal	25	16	64.0	2	2	100.0
Bulbar-encephalitic	2	2	100.0	0	0	0.0
Bulbar-spinal-encephalitic	7	4	57.1	1	1	100.0
Total	55	29	52.7	5	5	100.0

that there is a close correlation between the extent of muscle weakness and continued physical activity after the onset of symptoms. Hargreaves [29] and Horstmann [30] have confirmed this.

Transportation of the acutely ill poliomyelitis patient over long distances may contribute to fatigue and may in itself be hazardous. This is especially true of the bulbar poliomyelitis patient, for whom there is the danger of emergency situations that cannot be adequately handled en route because of lack of equipment and trained personnel.

In our series of cases 15 of the 40 deaths occurred within 24 hr. after hospital admission; nine of these patients were transported to our hospital from outside

26. Wright, J.: The Respir-Aid Rocking Bed in Poliomyelitis, Am. J. Nursing **47**:454 (July) 1947. Lenarsky, M.: The Rocking Bed: Its Use in Poliomyelitis, Arch. Pediat. **66**:339 (Aug.) 1949.

27. These studies were made in association with Dr. Donald T. Whedon.

28. Russel, W. R.: Poliomyelitis: The Pre-Paralytic Stage and the Effect of Physical Activity on the Severity of Paralysis, Brit. M. J. **2**:1023 (Dec. 27) 1947.

29. Hargreaves, E. R.: Poliomyelitis: Effect of Exertion During the Pre-Paralytic Stage, Brit. M. J. **2**:1021 (Dec. 11) 1948.

30. Horstmann, D. M.: Acute Poliomyelitis: Relationship of Physical Activity at the Time of Onset to the Course of the Disease, J. A. M. A. **142**:236 (Jan. 28) 1950.

the city,[31] some from camp and resort areas. It was our impression from their histories that they were not so ill when they began the trip. It is possible that the clinical course might have been the same otherwise. There were other patients who had been transported over long distances without similar termination. However, the clinical course of these nine patients was a striking feature and gave emphasis to the factor of transportation over long distances during the febrile period as possibly contributing to the severity of involvement and to mortality.

SUMMARY AND CONCLUSIONS

The significant clinical and pathological findings in 526 cases of poliomyelitis are presented and discussed.

There were 40 deaths; 39 were of patients with bulbar involvement. Complete vascular collapse resulting from failure of the vasomotor center accounted for 33 deaths (82.5%). The availability of the respirator for respiratory difficulty due to peripheral or central failure and the use of central stimulation for the latter minimized fatality from these causes.

Vomiting of coffee-ground material, considered an unfavorable prognostic sign, occurred in 16 patients with bulbar poliomyelitis, 11 of whom died.

The pathological findings in the gastrointestinal tract are noted. One patient showed a postmortem autolytic perforation of the fundus of the stomach. Reference is made to reports of peptic ulceration accompanying bulbar poliomyelitis.

Muscle pain was not a predominating feature in this series. The response to hot packing was satisfactory. Drugs for the relief of pain and muscle tightness did not prove effective.

Experiments in therapy with an antibiotic drug, an antihistaminic agent, and a refrigeration apparatus are mentioned.

The treatment of bulbar poliomyelitis patients is discussed. The use of drugs for vital center stimulation was effective in some instances. Six tracheotomies were performed, and all six patients died.

The use of the respirator is discussed. Bulbar involvement was not considered a contraindication to its use. Weaning of patients from the respirator was started early.

Transportation of the acutely ill poliomyelitis patient over long distances ("transportation fatigue") may contribute to the severity of involvement and to mortality.

Dr. Vera B. Dolgopol, Pathologist to the Willard Parker Hospital, gave suggestions in this study.

31. Brahdy, M. B., and Katz, S. H.: Effect of Transportation on Severity of Acute Poliomyelitis, J. A. M. A. **146**:772 (June 30) 1951. Lenarsky.[24]

NASAL, NASOPHARYNGEAL, AND THROAT SUCTION APPARATUS FOR THE NEWBORN AND SMALL INFANT

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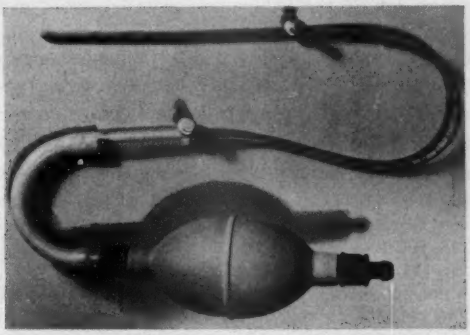
REMOVAL of excessive quantities of foreign material, such as mucus, blood, or regurgitated formula, from the upper respiratory passages of infants is not a new problem. In the hospital suitable suction apparatus for this purpose is usually available, but in the home or the office, when faced with emergencies, the pediatrician often has no quick, safe, and adequate source of suction.

Because it was recognized that in such difficult circumstances a conveniently portable and inexpensive suction apparatus might well be lifesaving, the bulb suction apparatus was developed. It is neither too bulky nor too expensive for ownership by the practitioner.



Portable infant suction apparatus. (The two aluminum pins are not a part of the apparatus.)

APPARATUS

The apparatus (Fig.) [1] has been designed as simply as possible in order to aid the physician working alone and to facilitate cleaning and care of the equipment. It is composed of a round-tipped, multiple-opening catheter which is attached to the suction bulb by a glass adapter. The catheter has a consistency and diameter which permit it to be passed easily through the nose with minimal chance of damage to delicate membranes. A secretion trap may be substituted for the glass adapter if the amount of material is excessive or if it is desirable to save a sample for culture or other study. The bulb itself is designed to give an adequate and safe amount of suction at the catheter tip.

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1. The suction apparatus described in this article is available at The Foregger Company, Inc., 55 W. 42d St., New York 18.

The same bulb may be used for actual intratracheal suction by substituting for the glass adapter a brass adapter which is made to hold suitable lengths of No. 11 F. ureteral catheter. The technique of this procedure has been described previously.[2]

TECHNIQUE AND USES

No special skill is required for inserting the catheter into the upper respiratory passages. The instrument is simply passed through the nostril to the desired depth in the hypopharynx. For the removal of excessive secretion other than saliva, it is important to insert the catheter via the nose, because small infants in the prone position, or even upright, tend to drain nose, mouth and nasopharynx into the back of the throat, and, unless moribund, they are well able to fight peroral insertion of the tube. Once the catheter has reached the desired site, the operator needs only to pump the hand-suction bulb until he is satisfied that the airway has been cleared. It is well to point out that this procedure is not a substitute for intratracheal suction,[2] nor will it be lifesaving for patients who have actual congenital anomaly at the level of the larynx or below.[3] Bronchoscopy will be needed urgently for these patients, who, fortunately, are few.

The apparatus has another very practical use. It provides an excellent method for cleaning out excess secretions in a child's nose prior to routine examination. For this purpose it is quick and gentle, and it is not usually upsetting to either the patient or the parent if the child is allowed to handle the suction bulb himself.

SUMMARY

1. A safe, easily used, and easily portable suction apparatus for the removal of excess secretion from the upper respiratory passages of the newborn and small infant is described.

2. The limitations of the apparatus are pointed out.

3. Attention is called to the use of the apparatus in routine examination.

26 Strathallan Park.

2. Emerson, E. B., Jr.: A Safe and Positive Method of Tracheobronchial Aspiration in the Newborn, J. A. M. A. **144**:613 (Oct. 21) 1950.

3. Heatly, C. A., and Emerson, E. B. Jr.: Bronchoscopy in the Newborn: An Analysis of 50 Cases, Ann. Otol. Rhin. & Laryng. **57**:802 (Sept.) 1948.

Progress in Pediatrics

THE VALLEY OF THE SHADOW OF BIRTH

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I. FULL-TERM BIRTH

THE ENGLISH writer Elizabeth Bowen [1] points out in a recent essay that to most people the golden days of the past are not those of very long ago. We can so little imagine the life of 1750 (or even 1850) that it casts no spell over us. On the other hand (says Miss Bowen), the "near" past, the days when our fathers or our grandfathers were boys, the days which our own lives almost overlap—most of us would say those were the days when it must have been especially good to be alive.

Those were the days of some 60 years ago when Benjamin Knox Rachford began his medical work in Cincinnati. Not in the too distant and unimaginable past; not in the frustrating present. How attractive they look to us now! Think of the opportunities open to a young man at that time. Think of the scientific discoveries we might have made. If (equipped with only a little of our present knowledge) you and I had been launching medical careers 60 years ago, consider what microorganisms we might have been the first to identify, what immunological facts we might then have proceeded to elucidate about them, and finally, in the wise maturity which we would so gracefully have worn about 1925, think what chemotherapeutic and antibiotic agents we might have perfected long before Florey and Fleming. Indeed, we sigh, those were the days.

At this distance it is not only interesting but reassuring to consider the achievements of Dr. Rachford.[2] In the field of scientific investigation he made his contributions, firm and fundamental ones, regarding the processes of pancreatic digestion. He did this with the information and instruments of the 1880's. It seems peculiar to us now that he worked equally hard, or harder, over the relations between a miscellaneous group of disease conditions on the one hand and certain odd products of protein metabolism on the other. His 10 or 15 papers on the subject of these "leucomains" as toxins now seem a little off the track of medical progress. But to him and his colleagues they must have represented problems as interesting as those of pancreatic digestion. In any case, his energies were also being devoted to medical activities of a different sort. As a result, his laboratory contributions were not, I believe, Dr. Rachford's greatest services to medical progress. He had the broader vision, which saw how educational and philanthropic effort might be

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Benjamin Knox Rachford Lectures, delivered at Cincinnati, Feb. 6 and 7, 1951.

From the Department of Pediatrics, Harvard Medical School, and the Boston Lying-in Hospital and Children's Medical Center.

1. Bowen, E.: Once upon a Yesterday, Sat. R. Lit. **33**:9 (May 27) 1950.

2. Dreyfoos, M.: Dr. Benjamin Knox Rachford, 1857-1929, J. Med. **10**:228 (July) 1929. Lyon, R. A.: The Medical Contributions of Dr. Benjamin Knox Rachford, read at the Pediatric Seminar, Cincinnati General Hospital, May, 1929.

combined with the medical knowledge of his time to reduce the incidence of disease and death among a city's children. His active public life proved that his vision was correct and set a mark in child health by which many another city as well as many another medical school than his was measured thereafter.

Thus, those of us tempted to doubt whether scientific discoveries can now be made with our own woeful ignorance of mathematics and biophysics may take heart from the life of Benjamin Rachford. Medicine is not advanced only by the man in the laboratory. Dr. Rachford did advance medicine there, but by awareness of the large problems around him, by patience, work, and the optimistic spirit that brought out these same attributes in others, Dr. Rachford advanced it on a broader front. Because he and other pioneers turned their efforts so successfully to the protection of infants and children, there is now less work for us to do in those age groups. Should we not turn with equal energy to others—among them the newborn and unborn?

The general title: "The Valley of the Shadow of Birth," is perhaps as apt an image as any for the relatively brief but hazardous period lying between the phase of human life which culminates in a viable fetus and the phase which begins with an infant firmly adjusted to extrauterine existence. Perhaps we may think of the territory usually cultivated by pediatrics as bounded by this Valley on the east, just as adolescence closes our westward prospect with a vaguely terrifying region of jagged and romantic mountains. Let us in imagination take a brief excursion to the eastern horizon of pediatrics. From this vantage point, we may perceive still further to the eastward the dimly outlined plateau of antenatal existence, descending—here precipitously, there gently—to a dark river far below us. On the near side of the river the ground rises sharply again to the familiar territory at our feet. Figuratively speaking, we are looking into the Valley of the Shadow of Birth. The descent facing us is the period between what we call "viability" and delivery itself—which we may symbolize by the perils of the river. The ascent to our own familiar landscape is the so-called "neonatal period."

A never-ending army of women is descending the opposite slope. At some spots the terrain is more difficult than at others, just as the river which must be crossed is deep and turbulent in some reaches but in others offers little more than a shallow ford. Each woman is carrying a baby—some two, or even three. Although they are carried down the hill and through the river, the infants must scramble up the near side of the Valley as best they can, steadied to some extent by the mother's hand. The success of the infants is not assured until they reach the level ground on which we stand.

Had we posted a sentry at that particular section of the Valley traversed by Massachusetts mothers and infants (like terrestrial New England, a mixture of beautifully gentle with rough and forbidding country) he would report that just about 100,000 Massachusetts women crossed the Valley in the year 1949. In that year almost 60 of them—six in every 10,000 women—fell on the way, either in the descent of the opposite side, in the angry water of the river, or on the climb up to where we stand, which, here and there, is dangerously steep even for a grown woman. Six in 10,000 was not many; so recently as 1935 the number was more than six times as great. Yet they were young women, and not easily spared. Still, it is interesting—though quite understandable—to consider how much more of the

layman's concern has always been expended over the plight of the mothers than upon that of their infants, for whom the Valley is a vastly more dangerous place.

We could have predicted that the journey would take a greater toll of the infants than of their mothers, but perhaps not a toll so great as the count kept by our observer indicates. Among each 10,000 of these infants. about 150 were lost either somewhere on the other side of the river or in its waters, and thus stillborn; another 150 survived the river but found the ascent of the near side impossible, so that they are listed in Figure 1 as neonatal deaths. All told, in 1949, about 315 in each 10,000 Massachusetts infants never emerged alive from the Valley. This is a smaller number than would be recorded from some other states, yet a larger toll than that of any later period of similar or even greater chronological duration. It is one lost infant of every 32 who started the journey and equals some 50 lost babies for each lost mother.

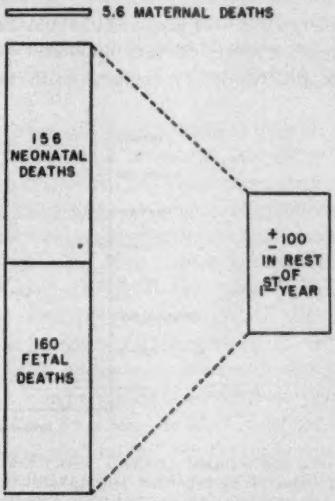

Fig. 1.—Comparison of maternal mortality (associated with pregnancy) and mortality of viable fetuses before and after delivery; losses per 10,000 potentially viable infants, Massachusetts, 1949 (data furnished by Dr. R. G. Rice, Division of Maternal and Child Health, Massachusetts Department of Public Health).

This metaphor has perhaps by now fully demonstrated (or even somewhat outlived) its usefulness. We may have to return to it now and then to emphasize a point or two. Before we take even partial leave of it, I would like only to recall that guerilla warfare tends to move up and down valleys, and within memory this one has been the scene of a good many skirmishes between Pediatric partisans on one side and Obstetric ones on the other. Since that ancient feuding became history and the occupants settled down to cooperative existence, the traffic across the Valley has become considerably safer.

The cooperation of obstetricians and pediatricians has grown from the obvious fact that one cannot consider stillbirths and neonatal deaths separately. Factors tending to alter the incidence of one seldom fail to affect that of the other. With

progress they tend to decline together, keeping reasonably near the proportion of one fetal death for each neonatal death.[3] In individual instances the relation obviously tends to be reciprocal. A maneuver may prevent the infant from being stillborn only to increase the likelihood that he will swell the list of neonatal deaths. Some evidence of this may be traced from the two lines in the left graph of Figure 2, which indicate that the neonatal death rate in New York City has not fallen as rapidly as the fetal death rate.

Because of this interrelation, the obstetrician cannot be (and of course seldom is) uninterested in the infant's condition once he has delivered it alive, nor has the pediatrician any right to be unconcerned with factors which may jeopardize the existence of the child only in utero. The more I see of the obstetrician's problems, the less do I feel I can advise him, the more do I feel I can learn from him. We are all in this together. As Dr. Irving, for many years obstetrician-in-chief of the Boston Lying-in Hospital, so forcefully put it: "A woman doesn't come to a maternity hospital to undergo a case of pregnancy; she comes to take home a baby." If she fails in this purpose, it makes no very important difference to her whether the failure is scored as a stillbirth or as a neonatal death, nor should it to us. Both

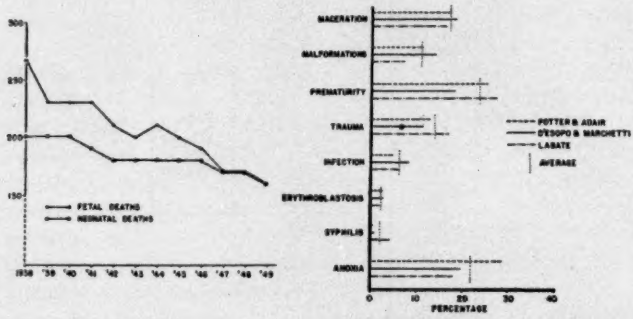

Fig. 2.—Left, rates of fetal and neonatal (under 1 week) deaths per 10,000 live births in New York City, 1938-1949 (data of Baumgartner and Erhardt [3]). Right, relative importance of eight factors responsible for fetal loss, summary of three statistical studies.[4]

are fetal losses, as good a name as any for casualties exacted anywhere in the Valley.

Discussion of the casualties occurring at any time after fetal viability will frequently involve matters with which the obstetrician is far more immediately familiar than I. My boldness in examining them comes from the opportunity of working for some years in daily contact with the staff of a good maternity hospital who have been generous in sharing with me not only their problems but their wisdom. Let them be assured once and for all that these lectures are offered to my fellow pediatricians in gratitude for that privilege.

An obvious approach to the problem of fetal loss is to find out what sorts of pathological factors or what clinical entities are largely responsible and to examine these in some detail. This is a fairly frequent form of medical exercise, and several

3. Baumgartner, L., and Erhardt, C.: Observations on Factors in Incidence of Prematurity and Stillbirth, presented at Conference on Pregnancy Wastage, sponsored by Committee on Human Reproduction, National Research Council, New York, 1951.

such analyses have been made within the past few years. The results show a remarkable degree of similarity. This must stem partly from the fact that statistical researches are not worth attempting except in hospitals with good records and with good pathological laboratories. In such hospitals good obstetrics is practiced. Apparently, a highly skilled obstetrical service comes up against about the same major problems in one city as in another and solves them with about the same degree of success. The findings of three analyses,[4] covering a total of about 3,000 fetal losses, are shown at the right of Figure 2. By a rough calculation, these 3,000 lives lost somewhere in the Valley must represent the casualties in some 100,000 pregnancies. The listing contains only eight headings, yet these eight essentially classify the things that can go wrong with a viable fetus before complete adjustment to extrauterine life. Some, such as erythroblastosis and syphilis, are quite specific. Others, such as anoxia and "infection," embody all sorts of possibilities.

Let us take up each of these eight categories as they must apply to our 300 or more lost infants in each 10,000 Massachusetts pregnancies. As to most of them I shall say little—for infections and erythroblastosis only a sentence or so. This will allow a rather detailed discussion of a few more or less controversial aspects of anoxia.

Certain of these groups actually have nothing to do with birth at all—particularly the highly unsatisfactory one entitled "macerated fetuses" or "maceration." Maceration is defined in the dictionary as "softening or wearing away by steeping"; the word correctly describes those physical (and predictable) changes occurring after the viable fetus dies, but it evades entirely the reason for death. The appearance of such a term among a list of causes of fetal death is a confession of ignorance, but at the same time, the expression of a knotty problem. To learn anything about these quiet cessations of life in utero is peculiarly difficult. Writers in the literature can scarcely be blamed for a tendency to shrug them off in the way we shrug off so-called acts of God as being no business of ours. A distinguished pathologist and embryologist of whom I sought information told me that, aside from the 25% or so obviously associated with toxemia, he had no explanation for the event which is followed by the process of maceration. He expressed the hope that the audience at these lectures would be entreated to send fewer macerated fetuses to the pathologist but more placentas from such pregnancies. The answer will probably be discovered, then, somewhere in the line of fetal food or oxygen supply. Until this answer is forthcoming, we shall simply have to record that if, as in other places, 17% of our fetal losses arise in this way, then of every 10,000 Massachusetts infants, some 50 or 60 never even make a start across the Valley. Those who would have been their mothers would like to know why.

If it is possible anywhere to approach the subject of congenital malformations with pleasure, it is possible to do so in Cincinnati. Few who were there will forget that meeting of the American Pediatric Society in 1942 to which your own Dr. Warkany first offered his elegant demonstration that at least some developmental abnormalities may represent the warping of normal genetic and early

4. D'Esopo, D. A., and Marchetti, A. A.: Causes of Fetal and Neonatal Mortality, Am. J. Obst. & Gynec. **44**:1 (July) 1942. Potter, E. L., and Adair, F. L.: Clinical Pathological Study of Infant and Fetal Mortality for a 10 Year Period at Chicago Lying-In Hospital, ibid. **45**:1054 (June) 1943. Labate, J. S.: Causes of Fetal and Neonatal Mortality on the Obstetric Service of Bellevue Hospital, ibid. **54**:188 (Aug.) 1947.

embryonic beginnings.[5] Here was evidence clearly embodying the idea of prevention. Once this new and hopeful concept had been demonstrated, Dr. Warkany proceeded to enlarge its scope and importance, by placing one beautifully fashioned piece of information upon another, preserving always both his sense of proportion and his sense of humor. On my return, in 1946, from investigating the results of wartime starvation upon the pregnant women of Holland, I had to tell Dr. Warkany that there seemed to have been no increased incidence of malformed infants born to these women six or eight months later. Indeed, the maternal undernutrition had commonly been accompanied by amenorrhea and temporary sterility, so that births of all sorts declined to a third of the number expected.[6] I remember the knitting of Dr. Warkany's dark brow over this somewhat unexpected development and then the sudden light which overspread his face as he said, "Still, could any congenital malformation happen to a person more serious than not to be conceived at all!"

In any case, with his experimental studies upon nutrition, with the almost simultaneous incrimination of maternal virus disease by the Australian workers,[7] and now with Dr. Ingalls' recent demonstration[8] of the specific effects resulting from brief exposures to anoxia, the whole problem of malformations is undergoing change and clarification. As yet there is little evidence that the frequency of malformations has been much lessened. Indeed, in recent years, as other causes of fetal loss are reduced, the percentage due to abnormality is increasing. Of each 10,000 in my own state, 30 or more infants still cross most of the Valley with relative ease, only to have it then revealed that they are in one way or another not equipped to sustain the conditions of life on this side. Time will tell to what extent we can reduce this number (and the much larger group who survive only for a more or less handicapped existence). That reduction will have begun with the work of Dr. Warkany.

The term "'prematurity," applied to about 25% of the fetal losses, does not by any means include all the lost infants prematurely delivered. It signifies only those in whom no pathological change more specific than the characteristic anatomy of the infant born too early could be found. The total number of premature infants would include at least 50% rather than 25% of the casualties; for this and other reasons, prematurity deserves a full discussion for itself alone.

Trauma associated with birth, infections in general, plus syphilis in particular, and erythroblastosis can all be dispensed with briefly here. The contributions of trauma and of infection to fetal loss are diminishing to a striking degree. If in any geographical area the incidences of birth trauma and neonatal infection have not declined during the past 20 years, it cannot be for lack of available information from elsewhere. The fundamental principles for reducing birth injuries and for preventing congenital syphilis and neonatal sepsis can be found in many articles and textbooks, and it is not necessary to repeat them here. Before leaving the subject of trauma,

5. Warkany, J.; Nelson, R. C., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency, Am. J. Dis. Child. **64**:860 (Nov.) 1942.

6. Smith, C. A.: Effects of Maternal Undernutrition upon the Newborn Infant in Holland (1944-1945), J. Pediat. **30**:229 (March) 1947.

7. Swan, C.; Tostevin, A. L.; Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, M. J. Australia **1**:409 (May 6) 1944.

8. Ingalls, T. H.; Curley, F. J., and Prindle, R. A.: Anoxia as Cause of Fetal Death and Congenital Defect in the Mouse, Am. J. Dis. Child. **80**:34 (July) 1950.

may I record my constant admiration for the skill and judgment of my obstetrical brethren in avoiding it and remark in passing that by the acquisition of this skill, modern obstetrics has solved its mechanical problems only to have its physiological ones loom the larger (Fig. 3). Erythroblastosis is quite properly in the hands of a special priesthood among us, and into their mysteries I do not easily enter. Certainly they have demonstrated their ability to reduce the incidence of neonatal death from incompatibility disease. How great is its contribution to the stillbirth group, and, perhaps, to the number of fetuses who never attain viability, remains to be discovered.

Everyone agrees on the increasing relative importance of anoxia, although it does not appear that all classify exactly the same entities under that heading. One man's anoxia is another man's atelectasis. Perhaps one man's atelectasis is still another man's hyaline membranes. Certainly the anoxia problem pervades all the others and must be considered in cases of malformed infants, premature infants, traumatized babies—and those without other handicaps. Conditions in which death is usually agreed upon as due primarily to lack of oxygen are responsible for at least 22% of our fatalities, or the loss of 70 of every 10,000 viable fetuses.

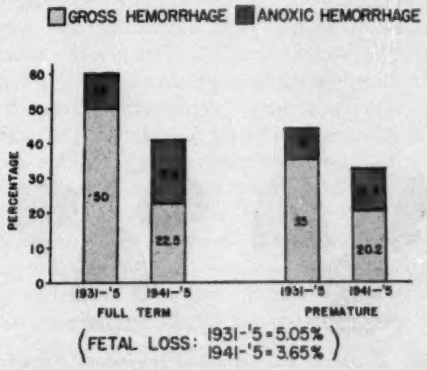

Fig. 3.—Comparison of traumatic with anoxic damage in live-born infants studied at autopsy at Boston Lying-in Hospital during two five-year periods (data from Dr. Arthur Hertig).

The circumstances of intrauterine life provide ample opportunities for interruption of oxygen supply. To reach the fetal brain, the proper number of molecules of oxygen at the proper pressure must be transported through the following channels or across the following structures: maternal airway, maternal pulmonary epithelium, maternal pulmonary vein, two valves and two chambers of the maternal heart, maternal aorta and other arteries, decidual vessels, essentially three layers of placental barrier, fetal placental vessels, umbilical vein, ductus venosus, fetal right atrium, foramen ovale, left atrium, mitral valve, left ventricle, aortic valve, aorta, and arteries and capillaries supplying the brain. This, it should be pointed out, is the short way. Some molecules may take a longer (and more scenic) route through the fetal circulation. Surprisingly enough, breakdowns in the transport system during fetal life are almost always located at certain critical regions more or less between the mother's body and that of the fetus: the placental site, placenta, and cord.

Once the act of delivery is accomplished, the pathways through the mother, the placenta, and the cord must abruptly be replaced by an unpracticed and immediately essential mechanism, consisting of the lungs and thorax. This is of itself helpless without proper nervous impulses originating in the brain, so that the peripheral apparatus of respiration is dependent on a central one. Conversely, the integrity of the central component will sooner or later deteriorate if the peripheral one is mechanically incapable of the sufficient respiratory exchange necessary to provide the brain with proper blood. Thus, just as we have found the lungs helpless without a properly functioning central nervous system, the central nervous system becomes helpless without properly functioning lungs (Fig. 4).

You are undoubtedly familiar with those situations—some obviously preventable and others relatively unpreventable—which by universal agreement will induce anoxia through either central or peripheral action. Let us, therefore, not dwell upon the dangers of incautiously administered analgesics and anesthetics, the pre-

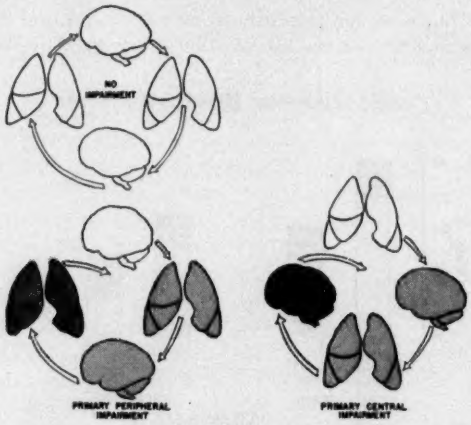

Fig. 4.—Interdependence of central and peripheral respiratory components, diagrammatic representation of relation between respiratory impulses delivered to lungs by brain and oxygenation of blood delivered to brain by lungs; shading indicates degree of impairment.

mature separation or abnormal implantation of the placenta, prolapse of the cord, difficulties peculiar to breech delivery, or the simple obstruction of the airway by mucus after any delivery. No one doubts the importance of each of these, nor is there any lack of well-founded and oft-repeated advice as to how their dangers can be reduced, as well as figures to tell us the degree of reduction at present possible.

Let us, therefore, risk discussion of a few more controversial matters: first, the problem of hyaline membrane formation in the lungs; second, the importance of postmaturity as an element in fetal loss, and, third, the question of Caesarean section as affecting respiration in the newborn infant. All of these, in one way or another, appear to come under the heading of "anoxia."

That "the position of the eosin-staining substance lying characteristically as a membrane along alveolar walls is simply the result of the mechanical dispersion of foreign material . . . by air violently inspired" was the conclusion of a

paper published in 1932 by Farber and Wilson.[9] Our own concept of the reason for hyaline material in the alveolar ducts and alveoli of newborn infants resulted from the researches of Farber, Wilson, and Sweet.[10] As a consequence of anoxic circumstances before or during birth, it seemed probable that excessive amounts of amniotic-sac contents would be aspirated and then subjected to the mechanical effects of subsequent respiration. So commonly could these formations, often called "vernix" membranes, be discovered in postmortem material from infants with a history of intrauterine asphyxia that we came to look upon them as an almost essential feature of certain autopsy protocols—necessary accompaniments of death after an insupportable crisis of intrauterine asphyxia.

In 1949 Miller and Hamilton[11] began a reexamination of the significance of hyaline membranes and offered the new concept that since (by their criteria) membrane formation need not be preceded by asphyxial or any other complications and is especially common in premature infants, it might be a reaction to an infectious agent. This set us—and others—to investigating the whole problem again. Our own material, collected under Dr. Arthur Hertig at the Boston Lying-in Hospital and reviewed by Drs. Wilhelm Blystad and Benjamin Landing, was from slightly more than 500 autopsies made during an eight-year period.[12] The results are too detailed for any formal presentation here. They did include the facts that about 25% of autopsies in full-term infants and 50% of autopsies in premature ones showed membrane formation. The material of the membrane was shown to our own satisfaction to be protein, and presumably amniotic-fluid protein. Its progress could be traced through the smaller bronchioles, either to ultimate flattening over the pulmonary epithelium or to impaction above that level with secondary atelectasis below. Squamous cells were rarely observed in association with membranes (or alone) in the lungs of prematurely born infants. On the other hand, squamous cells were commoner—and membranes rather less so—in the lungs of postmature infants. While membranes were never observed in the lungs of infants who were stillborn or less than 1 hr. old at death, they were also very rare in the lungs of those who died after living more than four days. Finally, contrary to Miller's experience, some complication capable of producing anoxia was usually found in the obstetrical history of full-term infants who showed membrane formation. Membranes appeared with more than expected frequency in deaths of either premature infants or full-term infants delivered by Caesarean section; some of these Caesarean sections had been performed only for disproportion as an elective procedure in normal pregnancies.

All this, and other experimental evidence ingeniously obtained by Dr. Landing from animals, seemed to substantiate the earlier hypothesis that membrane formation results from the effect of respiration in air after aspiration of a sufficient

9. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs: I. A Descriptive Study, Arch. Path. **14**:437 (Oct.) 1932.

10. Farber, S., and Wilson, J. L.: The Hyaline Membrane in the Lungs: II. An Experimental Study, Am. J. Dis. Child. **14**:450 (Oct.) 1932. Farber, S., and Sweet, L. K.: Amniotic Sac Contents in the Lungs of Infants, ibid. **42**:1572 (Dec.) 1942.

11. Miller, H. C., and Hamilton, T. R.: The Pathogenesis of the "Vernix Membrane," Pediatrics **3**:735 (June) 1949.

12. Blystad, W.; Landing, B. H., and Smith, C. A.: Pulmonary Hyaline Membranes in Infants, Pediatrics, to be published.

amount of amniotic-sac contents. It also indicated that premature birth (which I shall mention later), full-term birth attended or preceded by anoxic complications, Caesarean section, or postmaturity all seem to entail the danger of this course of events. In postmaturity the aspirated material apparently contains unusual numbers of squamous cells.

While these investigations of autopsy material were going forward, the staff watched with heightened interest the course of certain infants upstairs in the nursery. These infants usually had one special feature or another (and sometimes two or three) of those listed above in their birth histories. At delivery or soon after, their expiration was groaning or whining, and on inspiration a deepening furrow appeared at or below the costal margin or between the ribs. In small infants the whole sternum caved in. They appeared grim and anxious and seemed unable to rest or sleep, as though all their powers were required for the task of breathing. Physical examination of the chest showed the lungs sometimes emphysematous at first but soon presenting increasing areas of dulness and fine rales. You have all seen such infants, and they were not new to us, but we began to appreciate the specific cause of their symptoms, particularly as it became evident that if they survived for four days, these infants almost always then recovered rapidly and completely. If the respiratory difficulty was essentially the mechanical one of hyaline-plug or membrane formation (as we increasingly assumed), such obstructions were then not necessarily fatal but presumably could be resolved by absorptive or phagocytic processes gradually gaining the upper hand in the lungs. This conception led to considerations of possible physical therapy. The use of a respiratory atmosphere supersaturated with water, first advocated in our nurseries by Dr. David Gitlin, has been thought by some of our colleagues to offer mechanical relief; the same belief is increasingly held in other clinics.

Whatever name is ultimately applied to what our staff now rather loosely calls "hyaline membrane disease," we have been increasingly confident in the diagnosis of the condition and its degree in the living infant. Although therapy in a self-limited process of varied severity is extraordinarily difficult to evaluate, further experience may allow such evaluation and progress in treatment and prevention of this process.

The nonobstetrical writer approaches both postmaturity and Caesarean section a little warily, for his discussion must mainly be based on scattered clinical findings in occasional infants, rather than upon any regularly observed consequences of delayed or abdominal delivery. Particularly with regard to postmaturity is he hesitant. Toward that conception the obstetricians have been almost solidly sceptical, not only because its acceptance raises the question of greater dangers involved in induction of labor but perhaps also in self-protection against hordes of weary and impatient women a few days past the expected date of their confinement.

The literature on postmaturity seems to be concerned especially with the possibility that physical growth of the fetus may reach proportions incompatible with safe delivery. This eventuality may occur, but certainly rarely. On the other hand, the clinical acumen of my colleague Dr. Stewart Clifford has repeatedly enabled him to point out to us in the nurseries a clinically distinct type of infant often born some weeks after the due date and not necessarily of more than usual term weight. These infants may frequently be more than 21 in. (53 cm.) long. Their loose skin suggests not only relative dehydration but also the possibility that weight has

actually been consumed in utero. The vernix, skin, and cord are usually stained yellow or brown. The amniotic fluid surrounding them (and often pouring from the mouth and nose at birth) is also yellow or brown. Sometimes these babies are born dead, occasionally after auscultatory evidence of fetal distress. Those born alive (after labors quite normal aside from their dates) seem predisposed to respiratory distress.[13]

Many, if not all, of the unusual features of these infants could result from inadequate placental function. Our limited knowledge of the placenta indicates that at least in some respects its efficiency seems to wane as term draws near. Flexner and Hellman and their colleagues [14] have shown that human placental permeability declines after reaching its peak at 36 weeks; certainly sufficient prolongation of such a trend would place the fetus in increasing danger (Fig. 5). One cannot jump to conclusions from such evidence, for the Baltimore workers have also shown what enormous excesses of water and sodium normally traverse the placenta for each quantum left behind in the fetus. And yet one can scarcely avoid worrying a little over the state of permeability at 42 or 44 weeks. Barcroft and Young [15] found that when pregnancy in the rabbit is prolonged a few days past normal term, the placenta rapidly becomes unable to transmit enough oxygen to maintain the former saturation of blood reaching the fetal brain. If a fall in cerebral oxygen saturation of

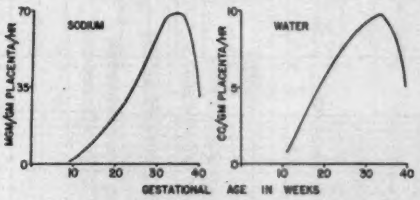

Fig. 5.—Human placental permeability, as shown by isotopic studies (adapted from illustrations of Flexner, Hellman, and associates [14] and reproduced by permission of the publisher).

comparable degree should occur in the postmature human fetus, the response would presumably include both passage of meconium and forced movements of a gasping character. A sufficient crisis of this sort would either cause death at once or produce central depression severe enough to interfere with any impulse to breathe at birth. The consequences of less severe intrauterine distress would be the occasionally observed symptoms of increasing postnatal respiratory distress from the obstruction of amniotic-fluid protein and squamous cells.

13. Clifford, S. H.: Fetal Anoxia at Birth and Cyanosis in the Newborn: Differential Diagnosis and Treatment, Am. J. Dis. Child. **76**:666 (Dec.) 1948.

14. Flexner, L. B.; Cowie, D. B.; Hellman, L. M.; Wilde, W. S., and Vosburgh, G. J.: The Permeability of the Human Placenta to Sodium in Normal and Abnormal Pregnancies and Supply of Sodium to Human Fetus as Determined with Radioactive Sodium, Am. J. Obst. & Gynec. **55**:469 (March) 1948. Hellman, L. M.; Flexner, L. B.; Wilde, W. S.; Vosburgh, G. J., and Proctor, N. K.: Permeability of the Human Placenta to Water and Supply of Water to Human Fetus as Determined with Deuterium Oxide, ibid. **56**:861 (Nov.) 1948.

15. Barcroft, J., and Young, I. M.: Internal Oxygen Environment of the Brain of Post-Mature Rabbit Embryos, J. Exper. Biol. **21**:70 (Jan.) 1945. Barcroft, J.: Researches on Pre-Natal Life, Springfield, Ill., Charles C Thomas, Publisher, 1948.

Certainly the majority of infants born a week or two past the expected date are not in any serious straits. Dr. Clifford has calculated that living infants with a frankly yellow vernix from meconium staining appear in our nursery about six times in 1,000 deliveries.[13] In 12% of such infants the birth has been postmature.

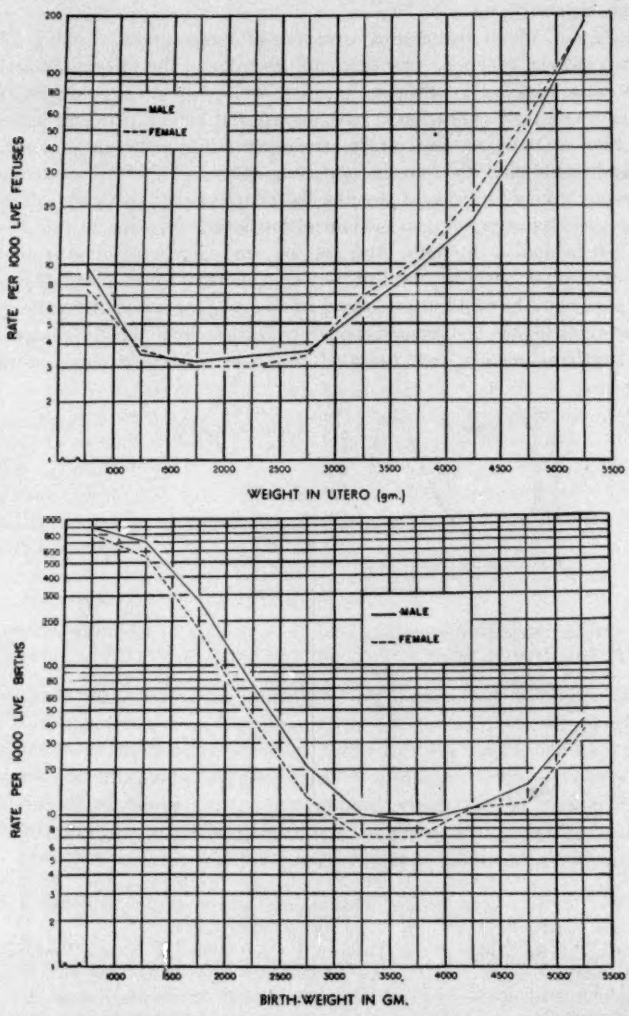

Fig. 6.—Upper, relation of weight to fetal death rate in New York City, 1939-1940; lower, relation of weight to neonatal death rate in New York City, 1939-1940 (from Baumgartner and associates,[16] by permission of the publisher).

Nevertheless, the pediatrician who becomes interested in noting expected dates of confinement will be more and more impressed by the mild dehydration, staining

of the cord, and occasional respiratory distress that appear among overdue infants. The relation of fetal loss to postmaturity as reflected by birth weight is suggested by charts recently published by Baumgartner and others [16] and reproduced in Figure 6. Faulty as information concerning menstrual dates may be, a large series of observations collected on that basis would be of interest. The available statistics [17] indicate that fetal loss rises after the 40th week.

Presumably the reason why certain infants are carried too long in utero will not be found until we know the cause of labor. It is interesting to note from the studies of Smith and Smith [18] that some 400 presumably normal, primiparous women treated with diethylstilbestrol during late pregnancy showed a 1% incidence of postmaturity, against an incidence of 3.4% in a group of otherwise similar mothers not so treated (Fig. 7). Whether sufficient postmaturity should, of itself, force the obstetrician's hand is a question usually answered with a qualified negative, on the basis that interference carries still greater risk to the baby than further expectancy. Even should this opinion prevail, the fact that the fetus can be harmed not only by crossing the Valley too early but also by crossing it too late is of some interest.

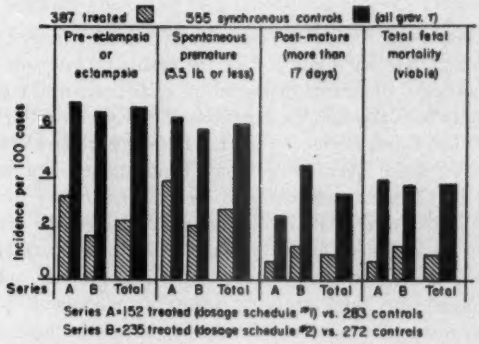
387 treated
555 synchronous controls (all grav. 1)
Pre-eclampsia or eclampsia
Spontaneous premature (5.5 lb. or less)
Post-mature (more than 17 days)
Total fetal mortality (viable)
Incidence per 100 cases
6
4
2
0
Series
A B Total A B Total A B Total A B Total
Series A=152 treated (dosage schedule #1) vs. 283 controls
Series B=235 treated (dosage schedule #2) vs. 272 controls

Fig. 7.—Influence of diethylstilbestrol on the incidence of late pregnancy complications, showing reduction in incidence of postmaturity (and prematurity) in two groups of primiparous women treated with two dosage schedules of diethylstilbestrol during pregnancy (after Smith and Smith,[18] by permission of the publisher).

If it be important that the crossing be attempted at the proper time, it also appears best that, if possible, it should occur by the traditional route. My colleagues and I agree with others [19] that the average infant slowly forced through the birth

16. Baumgartner, L.; Pessin, V.; Wegman, M. E., and Parker, S. L.: Weight and Fetal and Neonatal Mortality, Pediatrics **6**:329 (Sept.) 1950.

17. Clayton, S. G.: Foetal Mortality in Post-Maturity, J. Obst. & Gynaec. Brit. Emp. **48**:450 (Aug.) 1941. McKiddie, J. M.: Foetal Mortality in Post-Maturity, ibid. **56**:386 (June) 1949.

18. Smith, O. W., and Smith, G. V. S.: The Influence of Diethylstilbestrol on the Progress and Outcome of Pregnancy, Am. J. Obst. & Gynec. **58**:994 (Nov.) 1949.

19. (*a*) Russ, J. D., and Strong, R. A.: Asphyxia of the Newborn Infant, Am. J. Obst. & Gynec. **51**:643 (May) 1946. (*b*) Gellis, S. S.; White, P., and Pfeffer, W.: Gastric Suction: A Proposed Additional Technic for the Prevention of Asphyxia in Infants Delivered by Cesarean Section, New England J. Med. **240**:533 (April 7) 1949.

canal by any ordinary labor tends to have a more normal respiratory status than the average one rapidly lifted through an incision of the abdominal and uterine walls. Seemingly the difficulty is a consequence of the artificial delivery itself rather than of the general anesthetic often given, or of the mechanical or metabolic dilemma dictating the selection of birth through the abdomen. Let me say at once that in only some 6 or 7% of normal infants with the single obstetrical complication of a gentle and expeditious Caesarean delivery under spinal anesthesia is birth followed by any suggestion of respiratory disturbance. The point is that such signs occur in practically 0% of similar infants born through the pelvis. Why should the infant —all other things being equal—be less disturbed by crossing the Valley the hard old-fashioned way than by being whisked over it on a modern surgical bridge?

What we have fallen into the habit of calling "the post-Caesarean syndrome" may begin at once or appear an hour or more after the baby has been pronounced in good condition. If severe, the picture is essentially that described as associated with membrane formation. Much commoner are considerably milder and more transient manifestations, observed by those who look carefully for them; and in the great majority of infants delivered by elective section, no respiratory distress is noted at all.

As with our suspicions regarding postmaturity, we can suggest though not yet prove how abdominal delivery might induce the events occasionally occurring after section. The air passages of infants delivered by section seem to contain more fluid than those of infants born through the birth canal.[19a] Excessive fluid is also present in the stomach.[19b] Dr. Edith Potter [20] reported finding excessive cerebrospinal fluid in the subarachnoid space over the cerebral hemispheres in a large number of infants delivered by Caesarean section who died of respiratory disturbances associated with a hyalin-like membrane in the lungs. Although she originally believed the excess fluid in the meninges might be responsible for an increase in intracranial pressure which would affect the respiratory center and produce pulmonary embarrassment, the subsequent observation of identical pulmonary states in infants delivered by other methods who were without an increase in meningeal fluid makes it seem less probable that there is a direct relation between the two conditions.[21]

Presumably, extra fluid in the lungs and stomach is amniotic in origin. If so, it may be present before labor in the airways of all fetuses, and compression during transit of the birth canal may to some extent squeeze water from the baby born from below. At such deliveries fluid often flows from the nose and mouth while the trunk is still within the birth canal. Or (and I think this more likely) the sudden operative incision of the uterus and groping for the infant may stimulate reflex gasping and swallowing. The experimental physiologists have reported the extraordinary pains which must be taken in approaching the animal fetus in utero to circumvent its tendency to react thus to relatively minor peripheral stimuli.[22] A recent observation on twins coming to our nursery immediately after their Caesarean delivery, by Dr. Weston Sewall, is of some interest. The second infant had been

20. Potter, E., and Rosenbaum, W.: Association of Mild External Hydrocephalus with Death in the Early Days of Life, Am. J. Obst. & Gynec. **45**:822 (May) 1943.

21. Potter, E.: Personal communication to the author.

22. Barcroft, J.; Kennedy, J. A., and Mason, M. F.: Oxygen in Blood of Umbilical Vessels of Sheep, J. Physiol. **97**:347 (Aug. 5) 1940.

lifted from the uterus less than five minutes after the first. On aspiration, the stomach of the first twin contained clear fluid, that of the second contained bloody fluid.

Gellis and his colleagues have shown that prompt removal of the gastric contents after Caesarean section reduces the likelihood or degree of subsequent respiratory distress,[19b] so that if excess gastric contents (whatever their origin) are allowed to remain in the stomach, they may be regurgitated and aspirated. The so-called post-Caesarean syndrome thus seems to us essentially a mechanical consequence of aspiration, but of an aspiration resulting largely from the abnormal character of the delivery rather than from anoxic circumstances.

Our mortality among the 204 normal infants delivered by elective Caesarean section during the last five years was nil; a recent analysis of the records by G. B. Hutchison and R. L. Jones, two diligent fourth-year students, shows that untoward symptoms, all mild, occurred in 13, or about 6.5%, of them. This low incidence does not disprove the reality of post-Caesarean respiratory distress but may well result from our effort to avoid it. Infants so delivered have for some years been carefully drained by posture and suction before any attempts are made to encourage their breathing, and they are then sent to a special nursery adjacent to our premature nursery. There they are kept with the head below the level of the feet during an observation period of 24 hr. In the past two years gastric suction was added to this routine, but less fluid has been removable than that recovered by Gellis,[19b] perhaps because of differences in technique. We have never used the laryngoscope and have not felt it necessary to do so.

On numerous occasions the obstetrician will select Caesarean section as the safest course for the infant, and the mortality statistics indicate that the choices made by our own colleagues are consistently correct ones. Yet we respect the possibility of an extra hazard to the infant. If anticipated—and circumvented—this need not be alarming. But it should always be instructive. It suggests the advantages of attempting—whenever possible—to work with the mother and infant rather than for them.

What are the basic dangers that overshadow the Valley under consideration?

1. Unexplained death before the crossing is attempted.

2. Successful crossing by an infant improperly equipped for life on this side.

3. Damage from relatively unnecessary physical injury, from entirely unnecessary exposure to infection, or from a destructive agent unfortunately transferred to the infant from its mother's blood.

4. Interruption of oxygen supply from multiple potential causes, all of them more or less difficult to predict.

5. The accident of birth too early, the hazard of birth too long delayed, and the risk that artificial delivery, selected to avoid one danger, may introduce another.

Most of these have some flavor of the accidental about them, in the sense either that they are difficult to foresee or that they occur because of insufficient caution against the unlikely. The astonishing thing is that if these accidents are avoided by good fortune and good obstetrics (neither of which can ever entirely take the place of the other), all the remaining potential sources of trouble are so well handled by the infant. The full-term infant without congenital malformations, born of a normal, nonanesthetized mother with compatible blood, by any reasonably uncomplicated

pelvic delivery (and there are such babies), is almost sure to do well. Is this because there is nothing to go amiss under such circumstances? Scarcely. Consider the rerouting of blood streams in the circulation, the assumption of normal air breathing, the substitution of renal for placental regulation of the internal environment and of the unpracticed alimentary tract for the placenta as a source of food supply. In how many ways might any one of these processes go wrong? And yet how seldom is there reason to believe that it does so? The comparatively unerring way in which fetal physiological mechanisms go quietly about readjusting themselves to the conditions of extrauterine life is worth a parting comment.

When unpreventable accidents of one sort or another occur in the Valley of the Shadow of Birth and we intercede to help the infant, we should never quite forget that we are assisting an unexpectedly resourceful ally who may not yet have revealed all his strategy to us. Again, our main strategy should be to work as far as possible with him rather than for him. We may be forced by circumstances to interfere in the area of respiration; we are tempted to do so—though less than we once were—in the field of food and fluid administration, and the urge to meddle with the infant's endocrine economy is becoming almost irresistible. Actually, most of what has been done to reduce the dangers of the Valley of the Shadow of Birth at full term—and much has been done—has involved making all circumstances as favorable as possible and leaving everything else—which is almost everything—to the infant.

II. PREMATURE BIRTH

When Dr. Weech invited me to give these lectures, my first reaction was one of acute pleasure in being so highly honored. This unmixed gratification was short-lived. A little musing on the high level of medical scholarship in Cincinnati, the critical acumen of Dr. Weech and his department, and the standard set by preceding lecturers was enough to reduce me to the state of the Lord Chancellor, in Iolanthe, who found the compliment of his position to have its distinctly incovenient side. One of the inconveniences is Dr. Weech's sharp eye for inadequate or improperly presented data. He can always tell whether a speaker is fooling his public (or himself) by the skewness of a curve on his lantern slide. It has been relatively easy to avoid lantern slides with curves.

A more difficult problem is that Dr. Samuel Levine and Dr. Harry Gordon summed up their considerable knowledge of life after premature birth in two Rachford lectures just 10 years ago.[23] Those lectures were from the first classics. To their summing up of premature-infant physiology little has since been added, though many workers are in the field. My own ventures into metabolism bed studies have frequently brought me up against the unhappy fact that Levine and Gordon or Gordon and Levine had done the same thing—and better—many years before, and as this lecture was being composed, the same suspicion dawned again. Nevertheless, considering the fact that deaths among live-born premature infants outnumber those among full-term ones by almost exactly two to one in my own hospital, it was inevitably necessary to devote at least half of any program considering the Valley of the Shadow of Birth to this special group of infants.

23. Levine, S. Z., and Gordon, H. H.: Physiological Handicaps of the Premature Infant: I. Their Pathogenesis, Am. J. Dis. Child. **64**:274 (Aug.) 1942; II. Clinical Applications, ibid. **64**:297 (Aug.) 1942.

One fact that makes me rather happier about discussing prematurely born infants in the same series with the Levine-Gordon lectures was the preoccupation of those authors with the metabolic factors which determine how the premature infant will grow. Our own interest will be considerably more in those issues which decide whether the infant will survive to grow. For it is becoming clear that this fundamental question is decided early. Therefore, I expect to consider especially the early postnatal period during which the losses are concentrated. But before narrowing our focus down to a critical few days, I should like to range over the

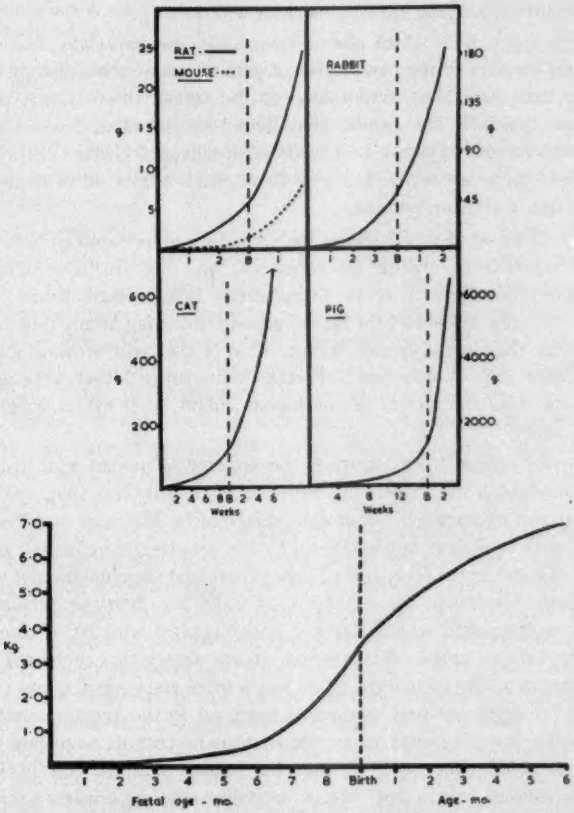

Fig. 8.—Upper, prenatal and postnatal growth curves (in grams) of five mammals, birth indicated by vertical broken line; lower, prenatal and postnatal growth curve (in kilograms) of the human fetus and infant; compare with upper diagrams (reproduced by permission of McCance and Widdowson [24]).

general field briefly and to look at two or three less frequently considered or newly reported factors applicable to premature extrauterine existence, both early and late.

One of these is the—to my mind—fascinating fact that so many human fetuses removed from the uterus many weeks too early can survive. Gestation can be curtailed at 75% of its normal span, and yet more than half the offspring can be

made to live. And if 80% of the gestation period is accomplished, at least three of every four prematurely born fetuses can be adjusted to extrauterine existence. Life in utero seems to be made up of three stages of about three calendar months each. The first encompasses the period of gross differentiation of organs. The second is the period largely devoted to the differentiation of finer structures in those organs. These two periods are obviously essential preparation for independent existence. But the third is a biological luxury—a three months' interval of extremely well-protected growth. And even if all of that interval is denied to 100 fetuses by extremely premature birth, some of them will live as infants. If the curtailment is of one month rather than three, almost all will do so.

An interesting exhibit which placed human life, and, especially, human prenatal and postnatal growth, in the perspective of general mammalian biology was shown by Dr. McCance and Miss Widdowson at the recent International Congress of Pediatrics in Zurich.[24] The exhibit represented an enormous amount of chemical analyses compressed into simple and easily comprehended charts. The authors have kindly allowed me to show you a few of these charts before all of them—I hope—appear in a future atlas or syllabus.

The first of these (Fig. 8) shows the strikingly more rapid growth after birth rather than before in the mouse, rat, rabbit, cat, and pig. In the next (Fig. 8) the human young is shown by contrast to make this rapid growth before rather than after birth. Actually, of course, the rate of growth in the pig at any time is enormous compared with that in the human infant. One of the most striking charts in the entire McCance and Widdowson collection demonstrated that although at birth the pig is one-third the weight of the human infant, at 9 mo. it weighs twice as much as a man!

If, as would appear from Figure 8, the upsurge of human fetal growth begins at an age of about 6 mo., when the fetus weighs a little less than 1,000 gm., the rapid growth can be shown by other data exhibited by McCance and Widdowson [24] to coincide with two clear tendencies: (1) the progressive reduction in the large component of water in the body and (2) the progressive accumulation of a surprising amount of fat. Obviously the 1,000-gm. or 2,000-gm. fetus or premature infant is relatively oversupplied with water and undersupplied with fat, if compared with the full-term fetus or infant. Nevertheless, it was shown that compared with many newborn mammals, the premature infant has a quite respectable quota of fat, while the average full-term one may contain as much fat as the average adult man. The more one looks at such comparisons, the more is he curious as to how the human species received this luxury of intrauterine infancy and the less likely is he to congratulate himself over a low rate of mortality among premature infants in his care. Nature seems to be so almost unnecessarily protective to these litters of one that we begin to wonder if the remarkable thing is not that so many premature infants survive but that so few do. The thought has its merits. One of the most successful approaches to premature infants as patients is with the conviction that they ought to survive.

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24. McCance, R. A., and Widdowson, E. M.: The Chemistry of Growth and Development, Exhibit Guide, Sixth International Congress of Pediatrics, Zurich, 1950; Brit. M. Bull. **7**:297, 1951.

In my curiosity about all of this, I have been attempting to learn something about the effects of premature birth in the larger domestic animals, but as yet without success. The circumstances of our veterinary brethren are sharply different from our own, for Professor Asdell, of Cornell University, answers my questions about horses and cows in a letter which concludes with the following:

> We do know that prematurity does occur and the distribution of gestation lengths follows a normal distribution curve. There have been occasional anecdotal reports of premature calves which have been raised, but the usual procedure is not to bother with prematures and a good many of them are knocked over the head as the farmer does not want to bother with the job of raising them. He also has the idea that undersized births will not grow normally and so will not produce profitable adults.

Although our discussion is not primarily concerned with this aspect of the matter, it should be made clear at once—apropos the above quotation—that prematurely born infants do produce desirable adults. Moreover, Dr. Clifford has repeatedly pointed out to us that many such infants carry a special value as being the only babies their mothers will be able to produce. In human biology we believe in bothering with prematures.

You may be disturbed by the assumptions used thus far as to the survival rate of prematurely born infants. Perhaps they sound overconfident. Actually, the mortality in any good maternity hospital is not very different from that in another and is—or can be made—practically nil after the first week from birth. This regularly obtainable later survival does not, I believe, depend on any one particular aspect of care so much as on skilled nursing and on the prevention of infections. Were one formula or one program of vitamin administration so much superior to another, I believe we would see more differences among the statistics of recognized clinics. But about the importance of circumventing infections and of providing expert nursing care, both early and late after premature birth, I don't believe enough has been said.

Certainly if one of us were faced with the (fortunately) hypothetical situation in which he had to choose between having a prematurely born child of his own in the charge of an excellent physician and an unskilled nurse or of an unskilled doctor and an excellent nurse, he would choose quickly and gratefully in favor of the latter team. A good nurse acquires—and imparts to her students who are learning to do the same thing elsewhere—an almost uncanny ability with these small patients. She somehow senses which infants can be relatively neglected and which must be almost constantly watched and stimulated. Infants in her care never aspirate their feedings. She often recognizes that an infant is not doing well before the doctor realizes it, and she develops infinitely tactful ways of making him find out that fact for himself. Her qualities are a mixture of love of her work, experience, and observation. Her training takes time but is worth it.

A program not only designed to eliminate infections but actually successful in doing so can have surprisingly good results, especially in reducing later deaths. A most instructive illustration, particularly so to me, for I watched it develop, was that reported by Dr. Stewart Clifford to the American Pediatric Society in 1949.[25]

25. Clifford, S. H.: Prevention and Control of Infection in Nurseries for Premature Infants, Am. J. Dis. Child. **79**:377 (Feb.) 1950; Infections of the Newborn and Premature Infant, Pennsylvania M. J. **53**:25 (Jan.) 1950.

Dr. Clifford based his report on the mortality in the premature nursery at the Boston Lying-in Hospital as compared with that in the premature nursery across the street at the Infants' Hospital. The nursery at the former hospital admits only infants born in its own delivery rooms. The nursery of the latter hospital admits infants born anywhere (except in the Boston Lying-in Hospital) in, and sometimes beyond, the metropolitan area. Both have for several years been under the care of the same visting physician and the same house officers. It was, perhaps, not surprising that the nursery at the Infants' Hospital had a mortality three times as great as that at the Boston Lying-in Hospital (Table 1), for we knew that babies doing poorly in other hospitals tended to be transferred to the Infants' Hospital, and we thought that the obstetrical experience provided for the Boston

TABLE 1.—*Comparison of Premature-Infant Mortality Rates at Boston Lying-in and Infants' Hospital Nurseries* *

Birth Weight, Gm.	Mortality, %	
	Boston Lying-in Hospital (1944-1948)	Infants' Hospital (1944-1947)
0 to 1,000 (0 to 2 lb. 3 oz.)	92	97
1,001 to 1,500 (2 lb. 4 oz. to 3 lb. 4 oz.)	58	66
1,501 to 2,000 (3 lb. 5 oz. to 4 lb. 6 oz.)	13	39
2,001 to 2,500 (4 lb. 7 oz. to 5 lb. 8 oz.)	5	31
0 to 2,500 (0 to 5 lb. 8 oz.)	16	50

* Data of Clifford.[25]

TABLE 2.—*Distribution of Ages at Death of Premature Infants at Boston Lying-in and Infants' Hospital Nurseries* *

Age at Death	Boston Lying-in Hospital, %	Infants' Hospital (1944-1947), %
0 to 7 days	96	68
8 to 21 days	4	13
21+ days	0	19
Total	100	100

* Data of Clifford.[25]

Lying-in Hospital premature infants was probably more favorable than that of some of the babies brought to the Infants' Hospital nursery.

In every weight group the mortality was higher at the Infants' Hospital nursery, but it was particularly disturbing that until 1948 almost one-third of the deaths in the Infants' Hospital premature nursery were among babies more than 1 week old (Table 2). Indeed, about 20% of the deaths were among babies who had been in the nursery more than three weeks. Review of the records suggested that the great majority of these late fatalities might be related to infection—sometimes not clear-cut, often not traceable to a definite source, and not in every case diagnosed until autopsy.

A carefully thought-out alteration in routine, largely devoted to improving current measures to check the spread of infection, was put into effect. Perhaps the most striking introductions were the isolation of each infant in an incubator with

its own individual supply of outdoor air and the administration of so-called prophylactic penicillin and sulfadiazine to practically every infant for at least seven days after its admission. The first year this new program was in effect the mortality fell from 50 to 36% and the next year to 23%. More impressive was the fact that deaths became limited to the first week. In passing, an unexpected by-product of this change of circumstances was the marked reduction in parenteral treatments. A number of body-fluid disorders that had formerly been considered the inescapable consequences of premature birth, but were revealed as largely the accompaniment of infection, were no longer seen in the nursery.

With these few comments on certain factors affecting survival of prematurely born infants after the immediate postnatal adjustment, we can use the remainder of our time in considering that critical earlier period. The data portrayed in Figure 9 were compiled from the records of the Boston Lying-in Hospital during the five years ending Jan. 1, 1950. They indicate the ages at death of the 249 premature

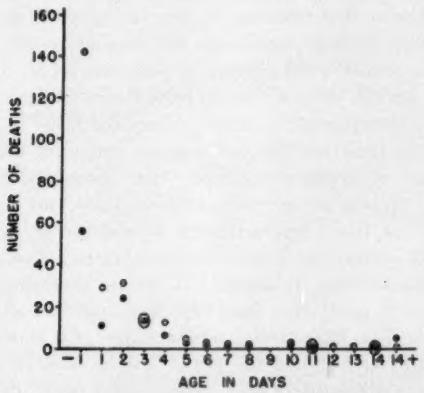

Fig. 9.—Ages at death of 377 infants dying in the neonatal period at the Boston Lying-in Hospital during 1945-1949 (249 premature infants, hollow circles, and 128 full-term infants, solid circles).

infants and the 128 full-term ones whom we lost (after live birth) during that interval. It should be pointed out at once that the similar concentration of mortality during the first five days in the two groups does not mean that a premature infant who is alive at 6 days is statistically as likely to go home in his mother's arms as is a full-term one of the same age. There are always less prematurely born than full-term infants at risk at any age in the hospital, for the 249 casualties represent about 1,800 premature starters, but the 128 were the losses in over 12,000 full-term infants. For every 100 premature infants born alive in the Boston Lying-in Hospital, about 15 died in the neonatal period. For every 100 full-term live births less than one infant was similarly lost.

It is no wonder that the premature infants find the ascent from the Valley so much more difficult than do their full-grown and relatively lusty companions of 40 weeks' gestation. But it seems to me interesting that the hazards at each level of the

ascent—those of each successive day after emergence from the river, which we have used to symbolize delivery—exact about the same relative proportion of their total toll in each group of infants. On the first day about half of the casualties occur; on the second—"B-Day plus one" in modern parlance—the same relative decline occurs in the two groups; each represents roughly 20% of the B-Day mortality. And on the next day each group has the same odd and perhaps meaningful little rise in fatalities. A slightly larger proportion of the neonatal deaths of full-term infants occurs after the fifth day. It may be splitting a very minute hair to say so, but all this suggests to me that our problem is not so much to get the premature infant adjusted to life as to get him adjusted to birth. I say this not in reproach against our obstetrical colleagues but in challenge to ourselves.

Before these data are evaluated any further, I should tell you that the 249 premature infants who died included 70 weighing less than 2 lb., or less than 907 gm., at birth. What to do with such infants is a statistical problem. In some clinics they would be charged off as nonviable. But, as Dr. Clifford likes to object, what then happens if one of them is uncooperative enough to live, as is occasionally the case? Perhaps because of that rejoicing in adversity which is one basis of the New England character, Dr. Clifford has always felt that we should leave such infants in our calculations as viable, and I am just as glad that we do. The essential result of removing them from this diagram would be to lower the open circle for the first day from 142 to 82. Everything else would change but little.

I am taking a long time over this one diagram because it seems to embody the crux of the problem of saving prematurely born infants today. The figures it portrays can be split up into any number of different analyses, with which my desk is littered, but none of these has been very informative to me. The underlying question posed by the open circles is whether saving more life on the first day would merely be losing more of it on the second. If the 142 premature infants who died within 24 hr. after birth could have been kept alive until the age of 5 days, would all but a small few of them have carried on thereafter? Or would one merely have postponed their deaths and shifted the peak? Put in another way, did only 18, or about 7%, of these prematurely born infant deaths occur after the fifth day of age merely because all but a small remnant of the infants incapable of living had dropped out before then?

In a sense the question may be looked on as an academic one. One factor in saving the lives of these infants, and a large one, is the temperament that forgets the thought that some premature infants will die, because of its preoccupation with the idea that any individual premature infant may live. If we are to foster that concept, we cannot flirt too seriously with the thought that preventing death may be merely postponing it. And, after all, short of the agriculturalist's philosophy, what else can we do but try to keep each of these babies going? A more serious question is whether any maneuvers designed to get the infant over the first day alive not only may be unnecessary but might actually make him less capable of getting past the second day. I must admit right away my inability as yet to work out any conclusive evidence that clearly answers that question from our own data or experience.

If we found any pathological entities which never were discoverable by autopsy in deaths of premature infants aged more than, say, 2 days, and if we knew we had some success in treating or preventing such conditions, then prevention of the early deaths from those causes would be an obviously indicated strategy.

The autopsies are summarized in Table 3. I apologize for their total number and can only tell you that the very early deaths of extremely premature infants were the ones most poorly represented. Nevertheless, the primary causes of death after premature birth in the more complete statistics of other workers, notably Dr. Edith Potter, are very similarly distributed, although I do not have her data as to the times of death. We may deal rapidly with the items which cause scattered deaths with no particular concentration at any one interval after birth. Erythroblastosis would not now bulk this large in such a table. Part of the period here represented occurred in those years when early delivery was still being advocated. Trauma is a small fragment and is growing smaller, while infections in a maternity hospital should be reducible today below the fraction here given.

What is called "prematurity," because it embodies no other outstanding pathological change listed below it in this table, was, as indicated, an explanation most commonly given by the pathologists for deaths during the first day, and two-thirds of the fatalities assigned to that cause occurred on that day. The majority of these deaths were of infants weighing less than 2 lb. I suspect that, aside from malforma-

TABLE 3.—*Primary Causes of Neonatal Death in 104 Premature Infants, Boston Lying-in Hospital, 1945-1949* *

Primary Pathology	%	Time of Death
"Prematurity"	28	Usually on 1st day
Anoxia	35	Rare after 4th day
Erythroblastosis	11	Scattered
Malformations	10	Scattered
Trauma	9	Scattered
Pneumonia	6	Scattered
Miscellaneous	1	Scattered
	100	

* Autopsy data of A. T. Hertig.

tions, this is perhaps the cause of fatalities in premature infants which we have least reason to believe we can permanently postpone. Until we can keep alive more than the present 5 or 10% of infants in this very premature group a little longer, even for three or four days, we do not have sufficient evidence to decide their fitness for further survival.

We are on somewhat stronger ground when we come to the deaths listed as primarily the result of anoxia. These occurred with decreasing frequency, so that less than 10% of them were found among the autopsied premature infants aged more than 4 days at death. The presence of so-called hyaline membranes, created in the peripheral portions of the lung as a result of extrauterine respiration following the intrauterine aspiration of amniotic fluid, was previously discussed at considerable length. It may be recalled that such formations were found twice as frequently in the lungs of premature infants as in those of full-term ones.[12] The essential role of aspirated amniotic-sac contents as a primary feature of this process suggests one line of approach to the reduction of anoxic fatalities.

Prematurely born infants may be likelier to form hyaline membranes either because they more commonly aspirate large amounts of amniotic fluid or because they have unusual difficulty in absorbing the residue of ordinary amounts of this

fluid from the bronchioles, alveolar ducts, and alveoli. In the former case, an increased aspiration presumably results because premature birth more commonly includes an anoxic hazard (as from too early placental separation) than does full-term birth. If the essential difficulty is with removal of what may be called normal amounts of amniotic fluid and protein reaching the bronchi and thence the smaller bronchioles, the fundamental fault may be in the infant's pulmonary circulation. Or, as a third possibility, the prematurely born infant may be no more apt to aspirate amniotic fluid in utero and no more wanting in absorptive mechanisms than the full-term infant normally is, but the premature infant may receive much less thorough drainage by posture and suction after birth than would be applied to a mature infant.

In any case, consideration might well be given to a delay in the traditionally rapid transfer of the prematurely born infant from the birth canal to an oxygen-filled incubator, to allow two or three minutes of postural drainage and catheter suction. Perhaps unnecessary haste has been devoted to getting these babies into extra warmth and oxygen in the least possible time after their birth. Were this speed absolutely essential to prevent death, we might expect that even with such precautions, a considerable proportion of our premature-infant fatalities would occur within the first hour because of insufficient speed in making this transfer. Actually, of our 249 deaths among prematurely born infants, only 15, or 6%, occurred so early. Even among the 140 fatalities among infants of less than 3 lb. (1,360 gm.) birth weight, death occurred within an hour in only 10, or 7%. The more one sees of such miniature organisms, or even of the certainly nonviable tiny fetuses operatively removed in the delivery room, the more does he sense that, like a character in a recent novel, they have "a rage to live." They do not die easily. Advantage may be taken, for a few moments, of that phenomenon to provide enough gentle drainage and suction so that their lives would not be handicapped by the advance deep into the lungs of aspirated material never again so easily removable as immediately after birth. If a supersaturated atmosphere can be proved of value in aiding any infant with this syndrome, it should cautiously be provided to premature infants in respiratory distress.

Previously I mentioned, but did not pause to discuss, the roles of anesthesia and analgesia in the production of deaths categorized as anoxic among full-term infants. My own belief is that in full-term deliveries pain relief may be of more benefit than harm, always provided this definitely two-edged sword is handled by a man who knows how to use it. When we consider the dangers of premature birth, ample evidence indicates that such deliveries should be conducted either with no anesthesia or else with some form which neither encroaches upon the prenatal oxygen supply nor dulls the responsiveness of the central nervous system after birth. So-called conduction anesthesia has been recommended as preferable even to no anesthetic at all, since it decreases the tendency to precipitate delivery by reduction of uterine contractions and relaxes the mother's pelvic floor—thus reducing in two ways the physical stresses affecting the baby. Masters and Ross [26] have recently published a comparison between the results of more than 200 premature deliveries with use of conduction anesthesia and those of a somewhat larger group of premature deliveries with use of all other forms of pain relief, including a few without any

26. Masters, W. H., and Ross, R. W.: Conduction Anesthesia: Protection Afforded the Premature Infant, J. A. M. A. **141**:909 (Nov. 26) 1949.

analgesia or anesthesia whatever. There were almost exactly half as many fatalities among the infants delivered with use of caudal and saddle-block techniques, the reduction being effected especially among deaths during delivery and immediately afterward. From these data we may infer that the percentages of premature neonatal deaths charged to simple prematurity per se and to anoxia could both be reduced by the skilled use of newer anesthetic techniques.

In our own nurseries, under the charge of Dr. Clifford, the problem of these critical postnatal days has been met, as everywhere else, by reliance on increased atmospheric oxygen, on humidity and warmth controlled so as to keep the infant's temperature steady, on protection against infection, and on the always essential nursing skill. To this general routine has been increasingly added a policy of omitting the intake of food or water for two or more days. The effects of this upon survival have seemed to us satisfactory though difficult to evaluate. In general, mortality has tended to fall over the last several years, as it has in practically every other teaching hospital, but clear evidence as to the contribution of this one policy of delayed feeding has not been yet obtained. We have certainly not been aware of an increase in fatalities either during the first 48 to 96 hr., or after the introduction of feeding.[27] The courses of infants given delayed feedings, and a certain amount of chemical data obtained from them, have raised a good many questions as to the

TABLE 4.—*Changes in Composition of the Human Body with Increasing Age* *

	Percentage of Water	mM./Kg. of Water		H_2O/N, Gm./Gm.
		Sodium	Potassium	
Fetus (5 mo.)	91	123	56	76
Fetus (7 mo.)	86	108	56	50
Newborn at term	80	98	61	42
Adult	72	67	94	24

* Based on data collected by Shohl.[29]

readjustment of water and electrolyte relations after premature birth and have hinted at a few of the answers.

In a paper published about two years ago,[28] for which the energy and imagination of Dr. Yudkin were to a large degree responsible, data were presented upon the losses and retentions of a number of premature infants. These suggested that the infant born before gestational maturity may have a relatively excessive amount of sodium-containing water in his body and a relatively (though perhaps not actually) diminished amount of body water associated with potassium, or intracellular water. One may—and should—ask at this point: "Excessive or diminished for what? For a 7-month fetus? Or for a full-term infant a few days after its birth?" I would have to answer by saying that the water, sodium, and potassium content of the prematurely born infant may be normal for him during intrauterine life and, if not abnormal for him when suddenly and prematurely born, abnormal for a mature infant soon after full-term birth. Table 4, largely based on data collected by Shohl,[29] brings out the background of these statements.

27. Delayed feeding has been shown to be unrelated to the subsequent development of retrolental fibroplasia in occasional premature infants discharged from our nursery.

28. Smith, C. A.; Yudkin, S.; Young, W.; Minkowski, A., and Cushman, M.: Adjustment of Electrolytes and Water Following Premature Birth (with Special Reference to Edema), Pediatrics **3**:34 (Jan.) 1949.

29. Shohl, A. T.: Mineral Metabolism, New York, Reinhold Publishing Corporation, 1939.

We believe that there are certain infants, born prematurely—and usually very prematurely—whose water and sodium contents are relatively excessive even for them, as 7-mo. or 8-mo. fetuses. These infants appear puffy with extra water; their hands and feet, if not pitting, are at least thick and without wrinkles over the knuckles of fingers and toes. For the majority of these infants no really objective proof of edema is available, though we believe our subjective impressions justify our calling them edematous. For some we have been able to accumulate balance data. Charts of the immediately postnatal chemical readjustment of four infants, two of whom appeared edematous at birth, are presented here.

The first chart, at the left of Figure 10, shows the cumulatively plotted balance data from an entirely normal and nonedematous full-term infant of 4,111 gm. fed as though he were a premature infant.

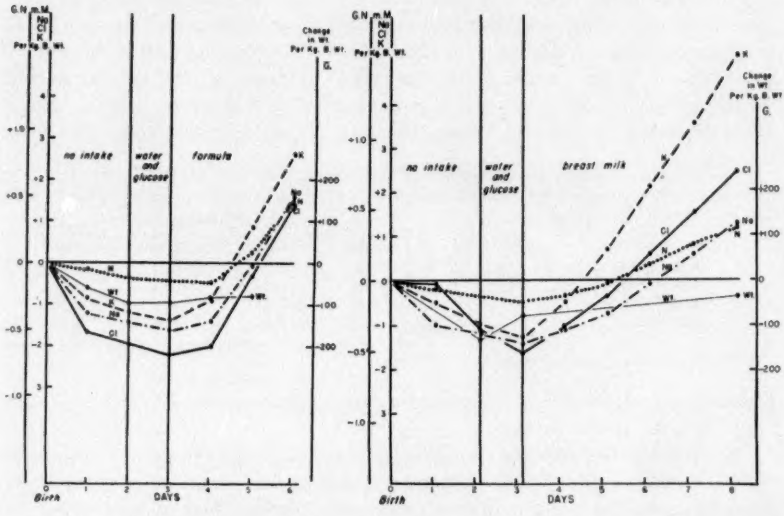

Fig. 10.—Left, cumulative daily balances of nitrogen, potassium, sodium, and chloride and cumulative changes in body weight of a normal full-term newborn infant (birth weight, 4,111 gm.) during the first six days after birth, plotted per kilogram of body weight, with nitrogen scale adjusted so that 1 gm. N equals 3.2 mM. of Na, Cl, or K (data of C. A. Smith and R. O. Roth). Right, cumulative balances of a normal nonedematous premature infant (birth weight, 1,530 gm.), plotted as in left chart (redrawn from data of Smith, Yudkin, and associates [28]).

For two days he was offered nothing at all; then water containing 10% dextrose was given for the third day, and beginning on the fourth day, an evaporated-milk formula. The amounts of these substances, per kilogram of birth weight, were comparable to those commonly given to our premature infants. The measurements in this and the following charts are all reduced to a per kilogram basis to facilitate comparisons.

I call your attention to the relatively similar losses and subsequent retentions of potassium, sodium, and chloride and the comparatively small negative nitrogen balance. Nitrogen is plotted in all these charts on a scale which represents, as nearly as can be estimated, its ratio to potassium in cells. Therefore, when nitrogen and potassium are lost or gained in the exact proportions they supposedly main-

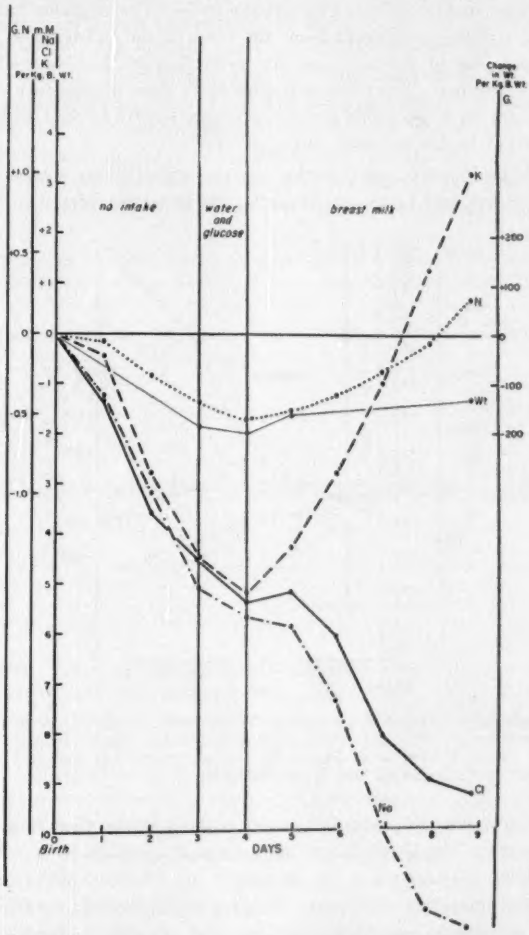

Fig. 11.—Cumulative balances of a premature infant (birth weight, 1,655 gm.) who appeared edematous at birth, plotted as in Figure 10 (redrawn from data of Smith, Yudkin, and associates [28]).

tain in cell fluid, the lines representing them should overlap, or, if starting from different levels, run parallel. In a general way, this full-term infant appeared to lose and then regain not only extracellular but also intracellular substances in fairly

constant relation. Six days after birth there was only 1 mEq. or so of scatter among the four items whose subtractions from or gains to the body we were tracing. In passing, the urine output of this infant during 48 hr. without water was 125 cc., which was less (per unit of surface) than that of some of our premature infants.

The next infant, whose balance data are indicated at the right of Figure 10, was a normal small premature of 1,530 gm. whom everyone considered as nonedematous as our smaller infants ever appear to be. The negative balances of this infant are not strikingly different from the ones of the full-term baby just mentioned, and, per unit of surface area, the urine volume was somewhat less than that of the full-term one. The retentions after birth show a difference which may be significant. Eight days after this infant's premature birth he had added potassium out of proportion to sodium and nitrogen.

The data of an infant of quite similar size and maturity are shown in Figure 11. This baby, who weighed 1,655 gm. at birth, was generally agreed to be edematous

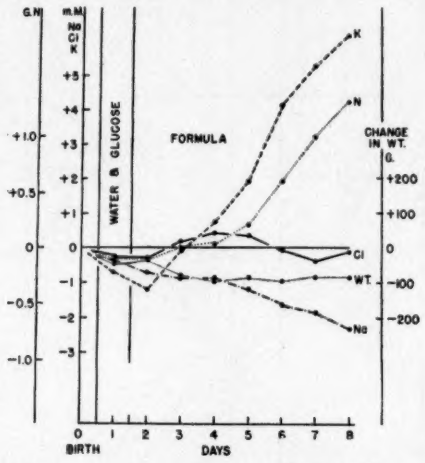

Fig. 12.—Cumulative balances of a premature infant (birth weight, 1,616 gm.) who appeared moderately edematous at birth and whose feeding was begun earlier than that of infants of preceding three charts, plotted as in Figure 10, all calculations per kilogram of body weight (unpublished data of C. A. Smith and M. S. Feinstein).

in appearance and was left somewhat longer without intake than was the preceding nonedematous one. The much larger but reasonably parallel losses of intracellular and extracellular electrolytes were contained in a urine volume approximately twice that of the preceding two infants. Feeding was followed by a sharp divergence in his dealings with the potassium, sodium, and chloride in breast milk, so that at 9 days the infant had acquired somewhat more potassium than at birth but was still rejecting the extracellular electrolytes.

The circumstances of collection of all these data bothered us in two ways—first, because some distortion of the expected electrolyte economy might have been introduced by the period of clinically prescribed fasting and thirsting, and, second, because the balances shown were constructed from intakes minus only

the outgoes in the urine. The stool losses were, as we later discovered, wrongly assumed to be inconsequential. Because of these possible sources of error, we were especially interested in the next infant, whose balances (Fig. 12) included both urine and stool and were thus complete except for the haunting difficulty of skin losses.

This infant was 1,616 gm. in weight and also moderately edematous. He was given water and dextrose from 12 to 36 hr. after birth and was then fed slowly increasing amounts of formula in exactly the same manner as our other premature infants had been fed, except that no postnatal dehydration period was allowed to occur. The sodium, chloride, and potassium divergence at 8 days, although not so extreme as that shown in the previous infant's less complete data, was in the same direction. The body-weight deficit was not quite, but almost, equal to that of the preceding infant at the same postnatal age, though the nitrogen retention of this infant, fed early, was for obvious reasons about 1 gm. above that of the infant who got no nitrogen-containing food till the fourth day. It is also of interest

TABLE 5.—*Urine Volumes During Postnatal Period Without Water or Food* *

Birth Weight, Gm.	Hours Without Intake	Urine, Ml./M.² Body Surface/24 Hr.
2,100	54	140
1,630	75	150
2,210	112	150
1,530	52	165 (Fig. 10, right chart)
1,960	60	180
1,650	52	210
2,270	72	270
1,690	69	300
1,660	69	300 (Fig. 11)
2,260	74	410
4,110	50	240 (Fig. 10, left chart)
Adult, ± 75,000	24	230 to 300

* Largely from data of Smith, Yudkin, and associates.[28]

that the upward slopes of nitrogen and potassium retentions are here running parallel, which suggests that earlier feeding may allow a prompter construction of protoplasm after birth. I am not sure that a few days' delay in this regard is a crucial matter.

This chart, which we hope to publish along with a number of other postnatal balance studies, seems to confirm the supposition that for some days after premature birth an electrolyte status which may be looked upon as normal for the 7-mo. or 8-mo. fetus in utero is being readjusted to one which is normal for the full-term fetus or infant. Very broadly stated, the fetus prematurely delivered tends to resemble a full-term infant recently given a large clysis of isotonic sodium chloride solution. Some, who appear to us edematous, for unexplained reasons seem to have much more salt and water at birth than do others, as their urine volumes also indicate (Table 5). The relation of all this to the fetal and maternal adrenal cortical hormones is at present regarded by me as an area in which angels fear to tread.

The entire chemical readjustment, of which these charts must give but small glimpses, is presumably not limited to those first four or five crucial postnatal days

which have formed the main subject of this discussion. We do not believe, from our autopsy and clinical data, that the explanation for any great number of neonatal deaths will be found in this particular area of biochemistry. Our observations do suggest to us that we need not hurry in the administration of foods or fluids after premature birth, and we assume that removal of the very real danger of food aspiration by delay in feeding makes the critical period a little safer, even when the nursing service is as skilled at gavage technique as ours has learned to be.

If we could find a way of preventing premature delivery, what a number of problems would be solved! In one way or another, about 50% of our neonatal mortality would presumably be eradicated, the tragedy of blindness from retrolental fibroplasia in occasional surviving premature infants avoided, weeks and months of expensive hospital care rendered unnecessary, and polite audiences no longer compelled to listen to long lectures on at least one subject. I cannot report to you that universally applicable means of prevention are at hand, but I can call your attention to some interestingly hopeful investigations.

TABLE 6.—*Results of Prophylactic Diethylstilbestrol Treatment for Premature Delivery on the Basis of Past Obstetric History* *

No. of Previous Premature Deliveries	No. of Patients	No. of Previous Pregnancies	Premature Deliveries		Fetal Deaths from Prematurity		Premature Deliveries on Diethylstilbestrol		Fetal Deaths from Prematurity on Diethylstilbestrol	
			No.	%	No.	%	No.	%	No.	%
1	36	56	36	65	32	89	15	41	7	47
2	22	46	44	96	32	73	13	59	5	37
3	12	41	36	88	27	75	6	50	2	33
4 or more	6	29	27	93	17	63	3	50	1	33
Totals†	76	172	143	..	108	..	37	..	15	..
Averages	..	..	..	83	..	76	..	49	..	40

* After table of Smith and Smith.[30]

† The total of fetal deaths was 133 among 172 previous pregnancies (77%) and 15 among 76 pregnancies in which diethylstilbestrol was given. There were 25 abortions in the past obstetric histories and none with diethylstilbestrol treatment.

For a number of years Smith and Smith, working at the Free Hospital for Women and the Boston Lying-in Hospital, have been unraveling the tangled skein of endocrinological events which occur during pregnancy. Without any attempt to go into the details of their studies, their observations may be summarized as indicating "a premature deficiency of the placenta in the secretion of estrogen and progesterone before and during late-pregnancy toxemia, premature delivery and intrauterine death." [30] The Smiths have emphasized "a reciprocal relation between vascular supply to the uterus and [this placental] hormonal support, adequate vascularity being as essential for the normal production of the placental steroid hormones as adequate hormonal support for the increased vascular demands of the pregnant uterus." [30] By careful and prolonged administration of the synthetic estrogen diethylstilbestrol as a stimulant to the placental secretion of sex steroids, these workers have attempted to combat one—and perhaps a most important one—of the contributory factors in uterine vascular deficiency.

30. Smith, O. W., and Smith, G. V. S.: Use of Diethylstilbestrol to Prevent Fetal Loss from Complications of Late Pregnancy, New England J. Med. **241**:562 (Oct. 13) 1949.

I have the permission of Drs. Smith and Smith to include here, from a large group of carefully collected data published by them, a few of their results which pertain to prematurity. Previously the reduction of postmature deliveries in a series of primiparas treated with diethylstilbestrol in late pregnancy [18] was mentioned. In Figure 6 are shown also the incidences of prematurity, as well as of other untoward results of pregnancy, in two study groups of primiparous women treated with diethylstilbestrol as compared with those of a synchronous control group. Diethylstilbestrol is expensive. Perhaps one should limit its use at first to those women whose history of prematurity in previous pregnancies is a warning that the same event may happen again. In Table 6 are the statistics of such a study [30] of 76 multiparous mothers whose former pregnancies had produced premature infants in 83% of instances. The reduction of premature birth among the infants of diethylstilbestrol-treated mothers that followed was not 100% but was still striking. The lower mortality among the 37 premature infants of the treated mothers suggests that those infants born too early nevertheless seemed to have greater vitality. This inference is supported by Table 6, which indicates a lower mortality among premature infants of treated mothers than would be anticipated by our current experience with infants of similar weight groups born to mothers not so treated. Finally, if, as is assumed, all this is the result of an improved blood supply to the uterus and placenta, one might expect that at unpreventable premature deliveries, and these of course do occur under diethylstilbestrol administration, the infants would be of better than expected weight and length. This expectation is supported by recorded measurements.[30]

I am aware that we are far from a single quick and easy procedure or group of procedures which will eradicate or even rapidly reduce the loss of life among unborn and newborn infants. It has been pointed out what the causes are and how some of them, such as fetal death without evident pathological change, or with pathological change successfully concealed by later events, are not even ready for attack by present knowledge. As to others, such as infection, trauma, erythroblastosis, and even some aspects of the anoxia problem, attention has been called to present trends which give hope for future progress. We have learned ways of making life relatively safe for the premature infant, although we still do not know how to make birth so. At least we know more definitely where to focus our efforts.

That there is no single, easy way to remove all these perils of the Valley of the Shadow of Birth should not too greatly deter us. Dr. Rachford, 60 years ago, had no single, easy way.

Abstracts from Current Literature

Chronic Infectious Diseases

TUBERCULOUS FOCUS ARTIFICIALLY CREATED (WITH THE AID OF KILLED OR ATTENUATED BACILLI): THE BASIS OF SUCCESSFUL ANTITUBERCULOSIS VACCINATION. G. SALVIOLI, Helvet. paediat. acta **2**:327 (Aug.) 1947.

In order to assure the specific effect of an inoculation, an inoculation illness of the type of that disease against which the patient is being inoculated must be produced. Salvioli states that on the site of the inoculation a histologically specific tuberculous process can be caused by a dead culture of tubercle bacillus (anatuberculin petragnani) and that a lasting allergy can thus be produced. In addition, Salvioli reports on 5,000 children who were inoculated according to the method of Petragnani and Salvioli. According to Salvioli's experience, an artificially tuberculous focus of infection with dead bacilli, and the resulting allergy, produces in children a kind of effective immunity.

FROM THE AUTHOR'S SUMMARY.

PRIMARY TUBERCULOSIS OF CONJUNCTIVA. H. STAMMBACH, Helvet. paediat. acta **4**:92 (Feb.) 1949.

A case of a patient completely cured of primary tuberculosis of the conjunctiva is presented. The following typical signs were found: (1) the process was unilateral; (2) there was involvement of the preauricular nodes and of other regional nodes; (3) there were no visible tuberculous lesions elsewhere, and (4) a small nodule of tuberculous tissue existed in the proximity of the supposed implantation point of tubercle bacilli.

FROM THE AUTHOR'S SUMMARY.

CHEMOTHERAPY OF TUBERCULOSIS: THE PHARMACOLOGY OF PARAAMINOSALICYLIC ACID, METHOD OF DETERMINATION, DISTRIBUTION IN THE ORGANISM AND RENAL ELIMINATION. L. RAGAZ, Schweiz. med. **78**:1213 (Dec. 18) 1948.

Neither the method of determination of paraaminosalicylic acid nor the results of the studies concerning its distribution in the organism and its elimination by the kidneys lend themselves to a short description. The student interested in these results will have to consult the original.

AMBERG, Rochester, Minn.

TUBERCULOSIS OF THE FEMALE GENITALIA IN CHILDHOOD AND ADOLESCENCE. E. FILLA and P. MARCONI, Arch. ital. pediat. e puericolt. **13**:48, 1949.

Nineteen cases of genital tuberculosis have been established post mortem in girls under 1 year to 16 years of age. The relative frequency, the pathogenesis, the anatomical character and the evolution of genital tuberculosis in children are studied, and the differential characters in comparison with the same disease in adult women are established.

FROM THE AUTHORS' SUMMARY.

A CASE OF TUBERCULOSIS OF THE ILIUM (JUXTACETABULAR), WITH ATYPICAL ROENTGENOGRAM. LEONARDO VALLETTI, Arch. ital. e puericolt. **13**:65, 1949.

The different aspects of tuberculous processes in the bone, especially in the pelvis, are discussed, and a description is then given of a case of osteolytic juxtacetabular lesion of the iliac bone in a 9 year old girl who showed only a mild symptomatology. The roentgenogram showed a cystic alteration with many cavities and polycyclic borders, without any surrounding decalcifications, and an undamaged articulation. A review is then given of the various morbid forms, which usually give similar characteristic roentgenographic pictures in this site.

The surgical intervention was explorative and curative; it consisted in a cleansing of the diseased cavity, which was a tuberculous focus, and the introduction of 20 mg. of streptomycin. The immediate result was excellent, and the following course was very favorable.

FROM THE AUTHOR'S SUMMARY.

THE CHRONOLOGICAL ASPECT OF CUTANEOUS REACTIONS AS A FACTOR IN EVALUATION OF THE DEGREE OF ALLERGY IN TUBERCULOUS CHILDREN. G. LODI, Clin. Pediat. **31**:137 (March) 1949.

The time element in the appearance and disappearance of the various phases of a positive tuberculin skin reaction is an important factor in evaluating the degree of allergy in children with tuberculosis.

HIGGINS, Boston.

BLOOD SEDIMENTATION RATE DURING STREPTOMYCIN TREATMENT OF CHILDHOOD TUBERCULOSIS. G. PARRINELLO, Minerva pediat. **1**:116 (March) 1949.

Periodic observations of the sedimentation rate of the blood of 23 children, 4 months to 11 years of age, over the course of one to seven months revealed that this test is a very good index of the clinical progress and prognosis in cases of tuberculosis under treatment with streptomycin.

HIGGINS, Boston.

LIPOLYTIC POTENCY OF THE BLOOD PLASMA IN CHILDREN ILL WITH TUBERCULOUS MENINGITIS OR MILIARY TUBERCULOSIS AND UNDER TREATMENT WITH STREPTOMYCIN. G. MURANO and CARMINE MELINO, Pediatria **56**:401 (July) 1948.

Observations on 33 children with miliary tuberculosis or tuberculous meningitis and under treatment with streptomycin revealed that the lipolytic potency of the blood plasma increased as the child showed clinical improvement and decreased as the child neared death. Determinations of the lipolytic potency of the plasma are of value in making a clinical prognosis in such cases.

HIGGINS, Boston.

LARGE SINGLE DOSES OF VITAMIN D_2 IN THE TREATMENT OF TUBERCULOSIS OF CHILDHOOD. E. SORAGNI, Pediatria **56**:420 (July) 1948.

Forty-nine children with various types of tuberculosis received single injections of 600,000 units of vitamin D_2; 11 other children received two, three or four such injections. In three of four cases of erythema nodosum there were a rapid regression of the skin lesions and a general clinical improvement. In 27 cases of tracheobronchial adenitis the fever was observed to fall by crisis; the fever returned in four cases but disappeared again after a second injection. In 17 of these patients there was marked clinical improvement; in five others there was some gain in weight. In three cases of adult pulmonary lesions no benefit resulted. In 14 of the 19 cases of pleurisy with effusion there was a regression of the symptoms by crisis; the other 5 patients were not benefited. In seven cases of disseminated miliary tuberculosis no clinical improvement could be detected beyond some slight gain in weight and appetite.

HIGGINS, Boston.

BLOOD SERUM PROTEIN IN TUBERCULOUS MENINGITIS DURING STREPTOMYCIN TREATMENT. G. COCOZZA, Pediatria **56**:475 (July) 1948.

The total blood protein in the serum of nine normal children averaged 7.13 gm. per 100 cc., of which 62 per cent was albumin and 32 per cent globulin, and the albumin: globulin ratio was 1.70 (1.60 to 1.90). Similar determinations were made with 21 children with various types of tuberculosis (meningeal, miliary, pleural or peritoneal) before and during treatment with streptomycin. The albumin: globulin ratio was lower in all cases of tuberculosis, varying between 0.70 and 1.50 (mean, 0.94). A rise in the albumin: globulin ratio signified a better prognosis in the patients receiving streptomycin.

HIGGINS, Boston.

ORCHITIS DUE TO ESCHERICHIA COLI IN AN INFANT TREATED AND CURED BY STREPTOMYCIN. A. DE BLASIO, Pediatria **57**:394 (May) 1949.

An infant of 12 months had had poliomyelitis with residual paralysis of the right arm and leg four months previously; this was followed by an attack of diarrhea and then by intermittent spells of fever culminating in swelling and marked tenderness in the scrotum. Sulfonamide and penicillin therapy was unavailing, but streptomycin resulted in complete relief of the condition in one week. A blood culture was positive for Escherichia coli.

HIGGINS, Boston.

VACCINATION AGAINST TUBERCULOSIS. RAFAEL FERNANDEZ CREHUET, Acta pediat. españ. **89**:491 (May) 1950.

In this article the author gives an exhaustive study of the use of BCG, discussing it under the following headings: (1) immunity and allergic reactions to tuberculosis; (2) various tuberculin tests; (3) types of vaccines; (4) techniques used; (5) effects of the protection by BCG, with review of the literature from all countries reporting; (6) influence of this protection on incidence of tuberculosis (new cases); (7) general health and development in infants given BCG, and (8) the time the BCG becomes effective and its duration. He also outlines the organization of an effective program in Spain.

ALLEN, Santa Fe, N. Mex.

A CASE OF TUBERCULOUS PERITONITIS. CARLOS HERRERA ROMERO, MAXIMILIANO SALAS M. and JOSE LUIS PEREZ NAVARRETE, Bol. méd. Hosp. inf., México **6**:44 (Feb.) 1949.

The authors present a case of tuberculous peritonitis in a 12 year old girl. The peritoneal lesion was considered a result of the generalization of the process. The respiratory route was considered as being the port of entry of the disease.

FROM THE AUTHORS' SUMMARY.

STREPTOMYCIN IN ABDOMINAL TUBERCULOSIS IN CHILDREN. RAUL MATTE, SERGIO IBANEZ and ALBERTO TRAUTMANN, Rev. chilena pediat. **19**:371 (May) 1948.

The authors report 10 cases of abdominal tuberculosis in which treatment was with streptomycin: 5 intestinal, 2 peritoneal and 3 of mixed form. This antibiotic has a rapid effect in abdominal tuberculosis; it shortens notably and reduces the clinical evolution. In some cases streptomycin was administered every four hours by intramuscular injection and in others every six hours. Treatment was successful, without general toxic symptoms. Only three patients continued receiving treatment; all the others were in good condition after a two to seven month control period. These results were obtained by giving less streptomycin than is given in other tuberculous disorders.

FROM THE AUTHORS' SUMMARY.

HYDROCEPHALIC SYNDROME IN TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. JORGE E. HOWARD, MARIANO LATORRE, ARMONDO DOBERTI and RODOLFO MERELLO, Rev. chilena pediat. **21**:337 (Aug.) 1950.

The authors studied 25 cases of hydrocephalus in children with tuberculous meningitis treated with streptomycin. This syndrome may appear any time during the course of the disease. By pneumoencephalography they determined that it can be produced by two mechanisms: hyperproduction of cerebrospinal fluid or lack of reabsorption due to the presence of an exudate in the basal cisternas. This second mechanism is commoner and has a worse prognosis. It is important to determine the type of hydrocephalus, as some of these patients can be improved by surgery.

FROM THE AUTHORS' SUMMARY.

ACUTE MILIARY TUBERCULOSIS IN A BABY OF SEVEN WEEKS TREATED WITH STREPTOMYCIN AND PARAAMINOSALICYLIC ACID. OSCAR CORREA B. and JULIO ALLIENDE A., Rev. chilena pediat. **21**:364 (Aug.) 1950.

The authors report an extremely rare case of cured miliary tuberculosis in a 7 week old infant. The diagnosis was based on a positive intracutaneous tuberculin reaction (2 + reaction to the Mantoux test, 1:100 dilution), recovery of tubercle bacilli on stained smear and by culture (gastric lavage), a typical roentgenographic picture of miliary tuberculosis and clinical symptomatology characterized by a temperature of 39 C. (102.2 F.), cyanosis, dyspnea, marked enlargement of the liver and spleen, pyuria and suppurative otitis media complicated by facial paralysis.

The treatment included administration of streptomycin (500 mg. daily initially and 400 mg. thereafter) and paraaminosalicylic acid (2 Gm. a day) for 6½ months and ample use of vitamins A, C and D and brewer's yeast. During the course of therapy there was an early beneficial effect on subjective symptoms. This was in contrast to the unchanged roentgeno-

graphic condition; the lesions in the chest began to improve six months later and then continued to improve until the complete recovery at the age of 2 years 3 months.

FROM THE AUTHORS' SUMMARY.

BCG VACCINATION: EXPERIENCE ON THE BASIS OF NEARLY 700 VACCINATED CHILDREN. K. BREU, Med. Klin. **26**:1129 (Sept.) 1950.

The BCG vaccination proved harmless except for eruption of a few minor transitory lesions, which conforms to the results of others. The author agrees with those who recommend, in order to assure the prevention of tuberculous infection an increase in the dose of the tuberculin to 1 mg., instead of 0.33 mg., as recommended by the Danish Red Cross. Vaccinated children should be protected from possible sources of infection from six weeks before until six weeks after the vaccination. The vaccination should be limited to certain selected groups, as has been outlined previously. On roentgen examination of at least 5,000 BCG-vaccinated children, so far none were found to have progressive endothoracic tuberculosis.

AMBERG, Rochester, Minn.

OBSERVATIONS CONCERNING THE PENICILLIN TREATMENT OF CONGENITAL SYPHILIS. W. REINHARD, Med. Klin. **36**:1133 (Sept.) 1950.

Twenty-three children with syphilis were treated with penicillin for 7½ days. Twelve of these were infants. The others were older than 1 year. For children under the age of 6 months, the penicillin was given by mouth; for children over this age, by intramuscular injection. The only side reaction was elevation of temperature to 40 C. (104 F.) at the start of the treatment. Syphilitic manifestations on the skin and mucous membranes healed quickly; bone lesions disappeared in two to four months. The blood serum became negative several months after the treatment.

AMBERG, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels, and Spleen

COMPRESSION OF THE TRACHEA OR ESOPHAGUS BY VASCULAR ANOMALIES: SURGICAL THERAPY IN 40 CASES. ROBERT E. GROSS and EDWARD B. D. NEUHAUSER, Pediatrics **7**:69 (Jan.) 1951.

Description is given of five different types of anomalies of the great vessels in the superior mediastinum which can produce compression of the esophagus or trachea (or both). These malformations of the vascular system can give rise to difficulties in swallowing and to serious disturbances in pulmonary ventilation. These anomalies include double aortic arch, right aortic arch with a left ligamentum arteriosum, anomalous innominate artery, anomalous left common carotid artery, and an aberrant subclavian artery.

The various symptom complexes which can be found with these anomalies are described. Endoscopic visualization of the interior of the esophagus or trachea gives valuable information in some areas. The investigation of these subjects should include fluoroscopic and roentgen studies of the esophagus and trachea by contrast medium. Data gathered from such roentgenologic examinations usually give a fairly clear idea of the type of vascular anomaly which is present.

It is possible to attack surgically each of these vascular malformations. In general, the esophagus or trachea can be relieved by division of an anomalous vessel or by displacement of an artery in such a manner that it is carried away from the compressed structure. When necessary, these operative procedures can be undertaken in very young babies, even in the presence of a high degree of respiratory obstruction. All the operations have been through a left anterolateral, transpleural approach, with the patient under general anesthesia with a closed system. The results of operation in 40 patients are analyzed.

It is evident that many vascular anomalies in the thorax which disturb the functions of the esophagus or trachea can now be treated with an excellent chance of relieving the obstructive symptoms.

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat, and Ear

OTITIS MEDIA IN INFANCY: TREATMENT WITH STREPTOMYCIN. HUGH A. CARITHERS, J. Pediat. **36**:767 (June) 1950.

Carithers treated five infants with otitis media caused by Pseudomonas aeruginosa. All were under 20 weeks of age, and none were severely ill. Streptomycin was given to these infants after penicillin and sulfonamides had apparently failed. On streptomycin administration they promptly recovered, even though the organisms in one case showed poor sensitivity to the drug in the laboratory.

MACDONALD, Pittsburgh.

CONGENITAL AURAL FISTULA. ROLAND B. SCOTT and CLINTON H. WOODING JR., J. Pediat. **36**:784 (June) 1950.

Congenital aural fistula is thought to be the result of incomplete fusion of the six primary tubercles which in the embryo are destined to become the external ear. The condition has a hereditary nature. The commonest type is found at the anterior margin of the ascending limb of the helix. If a fistula becomes infected and suppuration occurs, the sinus tract must be excised. In uncomplicated cases the tracts may be obliterated by fulguration or sclerosing agents.

MACDONALD, Pittsburgh.

EXTRANASAL TYPE OF NASAL GLIOMA. GEORGE V. MILLER and H. W. NEIDHARDT, J. Pediat. **36**:798 (June) 1950.

Miller and Niedhardt report an unusual case: a nasal glioma. The tumor was present at birth, was round, reddish, and moderately firm. It involved the right side of the bridge of the nose and extended to the inner canthus of the right eye. It measured 2 cm. in diameter. Removal was followed by uneventful recovery.

MACDONALD, Pittsburgh.

PENICILLIN AND ITS EFFECT IN PRODUCING A PREDOMINANT GRAM-NEGATIVE BACILLARY FLORA IN UPPER RESPIRATORY TRACT OF CHILDREN. FREDERICK D. HAFFNER, ERWIN NETER, and MITCHELL I. RUBIN, Pediatrics **6**:262 (Aug.) 1950.

A study was carried out on 90 children to determine whether conversion to a gram-negative bacillary flora of the nasopharynx and throat takes place during therapy with penicillin, either alone or in conjunction with sulfonamides, and to evaluate the influence of such a conversion on the course of the infection.

After the demonstration of "conversion" in 22 selected cases, a change to a gram-negative bacillary flora was observed in 30 of 68 unselected children. The gram-negative bacilli encountered in this conversion group included members of the Escherichia coli-Aerobacter aerogenes group, Pseudomonas aeruginosa, Alcaligenes fecalis, and Klebsiella pneumoniae; these organisms became predominant in 23 of the 30 cases. In 22 cases the gram-negative bacillary flora was present prior to commencement of specific therapy, but the number of these organisms increased in 13 instances. Such a conversion did not take place in 16 cases.

Vomiting per se was not responsible for the conversion, since it occurred more frequently in the nonconverted group, and vomiting was not a prominent feature of the converted patients. Of 10 patients receiving penicillin aerosol, in nine there was conversion to a predominantly gram-negative bacillary flora. The administration of sulfonamides in conjunction with penicillin did not materially lower the incidence of conversion. Clinical evaluation of the patients showed that on the average the children with conversion had a severer illness and one of longer duration than those of the nonconversion group.

Five patients of this group, all under 2 yr. of age, died. Autopsy was performed on four and revealed the presence of gram-negative bacilli in the lung tissue of three of them. This was considered indicative of the potential pathogenicity of this group of micro-organisms when they invade the respiratory tract.

The significance of these data is discussed.

FROM THE AUTHORS' SUMMARY.

Diseases of the Lung, Pleura, and Mediastinum

CONGENITAL CYSTIC DISEASE OF THE LUNG IN INFANTS AND IN CHILDEN. MARK M. RAVITCH and JANET B. HARDY, Arch. Surg. **59**:1 (July) 1949.

Twelve patients suffering from cystic disease of the lung are presented. They varied in age from 13 weeks to 13 yr. Some degree of infection was found in each case. Eleven of the 12 patients were successfully treated by surgical removal of the involved area of lung (six single lobectomies, four lobectomies of two adjacent lobes, and one pneumonectomy). The single death, from pneumonia, occurred in an infant of 8 mo. for whom operation had been deferred and was not performed.

Among these 12 patients, two were found to have cysts associated with anomalous lobes of the lung, in each instance a trilobed left lung; one of these had an anomalous arterial blood supply derived from the aorta. A third patient had an anomalous systemic artery entering a cystic lower lobe of the right lung. Resection of the cyst or of the cyst-bearing segment of lung is the recommended treatment.

FROM THE AUTHORS' SUMMARY.

ACUTE PULMONARY INTERSTITIAL AND MEDIASTINAL EMPHYSEMA (AIRBLOCK) AND PNEUMOTHORAX IN INFANCY AND EARLY CHILDHOOD. HAROLD ABRAMSON, GEORGE D. ROOK, and CORNELIUS NAU, J. Pediat. **36**:774 (June) 1950.

The authors discuss the probable pathogenesis of air block and present five illustrative cases. They point out that infants with unexplained acute respiratory and circulatory embarrassment, with dyspnea and cyanosis, may have pulmonary interstitial and mediastinal emphysema and pneumothorax. The diagnosis may be confirmed by roentgenography.

MACDONALD, Pittsburgh.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

INTUSSUSCEPTION DUE TO FAMILIAL ADENOMA OF THE SMALL INTESTINE. CARRINGTON WILLIAMS and CARRINGTON WILLIAMS JR., Arch. Surg. **59**:250 (Aug.) 1949.

Two case histories illustrating intussusception occurring in more than one member of a family as a result of familial adenoma of the small intestine are described. In both cases symptoms directly attributable to tumors of the small bowel were exhibited but were not recognized as such prior to operation for intussusception. The association of recurrent attacks of abdominal pain with secondary anemia should suggest the possibility of tumor of the small bowel.

KAISER, Rochester, N. Y.

INTUSSUSCEPTION ASSOCIATED WITH ABERRANT PANCREATIC TISSUE. JOHN L. KEELEY, Arch. Surg. **60**:691 (April) 1950.

A case of compound intussusception associated with aberrant pancreatic tissue in a 3½-yr.-old boy is presented. Resection of the portion of ileum containing the mass of heterotopic tissue was followed by end to end anastomosis, with recovery. Pathologic study of the specimen disclosed the pancreatic tissue to be located in the submucosal layer of the wall of the ileum. This appears to be the seventh instance of intussusception with intramural aberrant pancreatic tissue as the only regional abnormality.

FROM THE AUTHOR'S SUMMARY.

NONSPECIFIC MESENTERIC ADENITIS. HOWARD S. MADIGAN and ROBERT J. COFFEY, Arch. Surg. **60**:1122 (June) 1950.

This subject is thoroughly discussed as to etiology, pathology, and clinical manifestations. An anlysis is made of 184 cases at the Children's Hospital in Washington. The cases fell into two large groups, those in which symptomatic treatment was given and those in which surgical intervention was employed. The nonsurgical group consisted of 99 cases in which the clinical picture was sufficiently suggestive of mesenteric adenitis to make deferment of operative intervention safe. The surgical group numbered 85 cases; in these exploration was carried out, and in

most of them the preoperative diagnosis was acute appendicitis. A preceding infection of the upper respiratory tract, either tonsillitis or pharyngitis, occurred more frequently in the nonsurgical cases. No clear decision could be reached as to whether a case fell into the surgical or nonsurgical group.

KAISER, Rochester, N. Y.

ETIOLOGIC SIGNIFICANCE OF EVENTRATION OF THE DIAPHRAGM. WILLIAM C. BECK, Arch. Surg. **60**:1154 (June) 1950.

All the evidence points to the fact that eventration of the diaphragm is a congenital lesion. It appears that its main symptoms in the infant and child are those of respiratory embarrassment and cyanosis, in contrast to the milder adult gastrointestinal complaints. It is also possible that the condition is frequently missed and the symptoms ascribed to some other cause. It is becoming apparent that surgical correction of eventration can be safely and successfully performed.

The true incidence of eventration will not be discovered until extensive routine roentgenologic studies of newborn infants are carried out. All children who display symptoms of cyanosis or dyspnea should be studied roentgenologically, with eventration of the diaphragm considered as one of the reparable congenital defects.

FROM THE AUTHOR'S SUMMARY.

CARROT SOUP IN THE TREATMENT OF INFANTILE DIARRHEA. PER SELANDER, J. Pediat. **36**:742 (June) 1950.

Selander prepares carrot soup in the following manner: 500 gm. fresh carrots are washed and well scraped. They are then finely chopped and cooked with 150 gm. water in a pressure cooker for 15 min. The entire pulp is then passed through a fine strainer and diluted with hot water up to 1 l.; 3 gm. of table salt is added. The soup is made fresh daily. The soup is thick and must be administered by spoon, but it may be given to all infants, even to premature infants. The author claims that it is superior to all other types of oral treatment in infantile diarrhea.

MACDONALD, Pittsburgh.

CONGENITAL ANORECTAL STRICTURE. SAMUEL S. BROWN and AUSTIN H. SCHOEN, J. Pediat. **36**:746 (June) 1950.

The young infant who has colic, is constipated, strains at stool, or has small amounts of blood in his stool may have congenital anorectal stricture. Insert the lubricated finger into the rectum gently to make the diagnosis. Some infants with stricture will have no symptoms; only nine of 39 infants with congenital anorectal stricture in this study had shown symptoms. If untreated, the strictures will usually dilate spontaneously between 3 and 6 mo. of age. If there are associated symptoms, the stricture may be dilated with flexible rubber dilators lubricated with a liquid topical analgesic.

MACDONALD, Pittsburgh.

INCOMPLETE PANCREATIC DEFICIENCY IN CYSTIC FIBROSIS OF THE PANCREAS. GORDON E. GIBBS, WARREN L. BOSTICK and PEARL M. SMITH, J. Pediat. **37**:320 (Sept.) 1950.

The authors report two cases of cystic fibrosis of the pancreas, proved at necropsy. One patient had normal vitamin A absorption curves and duodenal trypsin concentration reduced but not reduced as much as is usually considered "typical" for the disease. The other patient had a normal duodenal trypsin concentration at 8½ mo. At 10 mo. the duodenal trypsin concentration of this second patient was below normal but still relatively high for this disease.

MACDONALD, Pittsburgh.

GASTRIC ULCER OF THE PYLORUS SIMULATING HYPERTROPHIC PYLORIC STENOSIS: REPORT OF A CASE IN AN INFANT NINE WEEKS OLD. ARTHUR R. C. COLE, Pediatrics **6**:897 (Dec.) 1950.

A brief review of the natural history of peptic ulcer in infancy and childhood is given. The symptomatology, differential diagnosis, and diagnostic procedures are presented. The diagnosis of peptic ulcer should be considered oftener in infants and children and the proper diagnostic procedures instituted.

A case of gastric ulcer simulating hypertrophic pyloric stenosis is presented. A summary of 31 cases with peptic ulcers found at autopsy at the Babies Hospital from Jan. 1, 1924, to Jan. 1, 1950, is given. From a summary of coexistent disease found in the autopsy cases at the Babies Hospital and reports from recent literature, it would appear that diseases of the central nervous, gastrointestinal, and respiratory systems are commonly present in cases in which peptic ulcer is shown at autopsy.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

VALUE OF CLINICAL AND SEROLOGIC TESTS FOR THE IDENTIFICATION OF UNIVITELLINE TWINS ONE OF WHICH HAD BEEN CHANGED IN ERROR. A. FRANCESCHETTI, F. BAMATTER and D. KLEIN, Bull. schweiz. Akad. med. Wissensch. **4**:433 (Dec.) 1948.

The parents of twin boys, becoming aware that the child of another family, born the same night in the same clinic, strikingly resembled one of their twins, contacted the authorities to determine whether or not a substitution had taken place.

Serologic, clinical and experimental biological examinations which were performed confirmed subsequently the supposition that an exchange had occurred. First, it was possible to demonstrate through Rh subgroups that one of the twins (Pierre J.) could not be the child of the supposed mother. On the other hand, blood groups of the second family's child (Eric V.) corresponded exactly with those of the other twin (Victor J.). In basing the studies on Siemens' polysymptomatic similarity method for twins, the authors were able to observe that the suspected twins, Victor J. and Eric V., not only presented a surprising similarity for all the somatic and psychomotor characteristics, but also had some identical anomalies (absence of the inferior central incisor teeth, daltonism). Finally, reciprocal transplantation of whole skin grafts performed on the three boys allowed them to furnish a biological proof of the identical twinning of Victor J. and Eric V. In fact, the grafts exchanged between Victor J. and Pierre J. demonstrated signs of necrosis, while those exchanged between Victor J. and Eric V. healed by primary intention. The results of the studies, therefore, left no doubt that a substitution actually occurred between one of the twins in the J. family and the child in the V family.

FROM THE AUTHORS' SUMMARY.

CONSTITUTIONALLY CONDITIONED CHANGES IN GRANULATION. A. ALDER, Schweiz. med. Wchnschr. **41**:1095 (Oct. 14) 1950.

The summary of this report states that so far all reported cases of granulation anomaly which were studied carefully were found associated with disturbances of the growth of bones. But the granulation anomaly is not the consequence of this disturbance; rather, it persists after cessation of bodily development. Maturation disorders of the blood leukocytes and of the bones are referred to the same injury. A gene injury due to consanguinity is of greatest importance. These abnormalities are observed in cases of gargoylism (Pfaundler-Hurler disease) and related diseases.

AMBERG, Rochester, Minn.

SOME OBSERVATIONS ON SALICYLATE THERAPY IN THE INFANT. G. MAGGIONI, Arch. ital. pediat. puericolt. **12**:267, 1948.

The absorption and excretion of sodium salicylate and of acetylsalicylic acid, administered orally and rectally in single or in repeated doses to normal and to rheumatic children, have been investigated.

The doses of the drugs required to attain a blood level of 25 to 35 mg. per 100 cc. should be from 0.12 to 0.18 gm. per kilogram of body weight. The simultaneous administration of sodium bicarbonate in varying doses is followed by a corresponding increased rate of excretion in the urine, especially in the first 12 hours.

In children under salicylic treatment the author observed (1) decrease of prothrombin in the blood without any direct relation to salicylemia (the hypoprothrombinemia quickly disappears after the drug administration is discontinued); (2) decrease of the ascorbic acid level in the blood to values of true hypoascorbinemia; (3) no variation of the pyruvic acid blood level.

A rational scheme of salicylic therapy for children is proposed by the author, who points out the determination of salicylemia as a convenient means in order to control the proper dosage of the drug, thus avoiding the dangers of overdosage. FROM THE AUTHOR'S SUMMARY.

BLOOD CONCENTRATIONS OF PENICILLIN FOLLOWING ITS AEROSOL ADMINISTRATION TO INFANTS. G. CALZETTI and M. LATO, Clin. pediat. **31**:143 (March) 1949.

Useful levels of penicillin in the blood may be obtained by aerosol administration of 30,000 units of penicillin every four hours. Masks were used with the infants, each administration lasting about 15 minutes.

HIGGINS, Boston.

PENICILLIN THERAPY IN DISEASES OF CHILDREN FROM AN EXPERIENCE WITH 122 CASES. N. CARRARA and B. KRAINER, Lattante **20**:65 (Feb.) 1949.

A 24 page article gives the conclusions drawn from the authors' experience with penicillin therapy in children. In general, large doses are recommended, especially for the small baby. In certain diseases other antibodies are recommended in addition to the penicillin, such as streptomycin in pertussis and a sulfonamide in meningococcus meningitis.

HIGGINS, Boston.

THE ANTISTREPTOLYSIN TITER IN THE SERUMS OF CHILDREN RECEIVING HYDROTHERAPY WITH MINERAL WATERS CONTAINING BROMIDES AND IODIDES. L. LANDUCCI, Lattante **21**:745 (Dec.) 1950.

A course of hydrotherapy using water containing bromides and iodides was found to be of benefit to practically every child with asthma or with enlarged or diseased tonsils. Of 90 children with hypertrophied or chronically diseased tonsils, the antistreptolysin titer of the serums was found to have increased in 23 patients and diminished in 47 patients after treatment; similar tests with 16 asthmatic children revealed an increase in four and a decrease in 10. In 25 patients on whom tonsillectomy had previously been performed, there was an increased titer in 13 and a diminished titer in nine.

HIGGINS, Boston.

ITALIAN CONTRIBUTION TO PEDIATRICS IN 1949. F. LO PRESTI-SEMINERIO, Lattante **21**:756 (Dec.) 1950.

A short sentence gives the substance of each of the 651 pediatric articles published in Italian during the year 1949. The most extensively treated subjects in this list are the streptomycin treatments of tuberculosis and of the blood dyscrasias, especially familial erythroblastic anemia (Cooley's anemia).

HIGGINS, Boston.

CONCENTRATIONS OF PARAAMINOSALICYLIC ACID IN THE BLOOD AND SPINAL FLUID AFTER ITS ADMINISTRATION BY VARIOUS ROUTES. A. CARNEVALE and S. CUTILLO, Pediatria **57**:364 (May) 1949.

At the end of two hours 0.1 gm. of the sodium salt of paraaminosalicylic acid given orally had led to practically the same concentrations of the substance in the blood and spinal fluid as when the same dose had been given intravenously or intramuscularly; the concentration in the spinal fluid rose as rapidly and as high with one method of administration as with another. Practically no paraaminosalicylic acid remained present in the blood 11 hours after the administration, although a near maximum amount was still present in the spinal fluid. Paraaminosalicylic acid is not found in the spinal fluid of children who do not have meningitis.

HIGGINS, Boston.

HYPOEVOLUTISM IN CHILDREN WITH REPORTS OF SOME CASES OF DWARFISM. W. TANGHERONI, Policlinico inf. **16**:389 (Sept.) 1948.

This article divides growth failure in children into the categories of hypoplasia, hypotrophy, hyposomia and microsomia and contains reports of five cases of dwarfism seen at the pediatric clinic in Pisa.

HIGGINS, Boston.

THERAPY WITH PENICILLIN AND PROCAINE HYDROCHLORIDE INTRA-ARTERIALLY. ANTONIO RIGHINI, Riv. clin. pediat. **48**:281 (March) 1950.

The good results obtained in the therapy of sepsis and osteomyelitis with penicillin and procaine hydrochloride injected into the arteries are described.

FROM THE AUTHOR'S SUMMARY.

COMPARATIVE STUDY OF PHTHALYLSULFATHIAZOLE AND SULFATHIAZOLE IN THE INFANT. CARLOS TREUER, Rev. chilena pediat. **20**:194 (May) 1949.

A comparative study of the blood and urine concentrations of sulfathiazole and phthalylsulfathiazole was made in 27 infants and one 8 year old boy. Both drugs were administered at the same intervals and in equal doses, to the same children.

The blood and urine concentrations of sulfathiazole tend to be high, with a great dispersion in the values (1 to 7 mg. per 100 cc.), while those of phthalylsulfathiazole are lower and more regular.

It is to be noted that the urine concentrations of phthalylsulfathiazole are lower than those of sulfathiazole, but in most cases within therapeutically useful limits.

No relation is seen to exist between the quantity of drug administered and the concentrations obtained. It also appears that neither the fluid intake nor the disease which afflicts the child has any influence on the concentrations.

FROM THE AUTHOR'S SUMMARY.

ACUTE LYE POISONING OF CHILDREN AS SEEN BY THE NEWEST STATISTICAL DATA IN HUNGARY. D. CSÖKE, Népegészségüy **29**:609 (Oct. 24) 1948.

Lye poisoning is a grievous problem in Hungary and is again the problem of the day. The number of acute lye poisonings of children, caused by accidents, has grown at alarming rate in the last years. On the basis of data collected from the territory of Budapest and the surrounding area, the author reports that fresh lye poisonings occurred in 69 children in 1945, 149 in 1946, and in 178 in 1947; all children were below the age of 14 years. In the country in 1945 there occurred 80 in 1946, 97 in 1947, 281 cases. These data, compared with old statistical data, show, surprisingly, that during these three years there were more lye poisonings than there were in the times when there were not any restrictions as to the use of lye. The Hungarian medical society fought for decades against lye poisonings and published propaganda of every kind against the use of lye. The interests of public provision and the problem of provision with soap render the situation more difficult and hinder what the medical society asks: the definitive and absolute prohibition of the sale of lye. The boiling of soap in the house has to be stopped. Only the manufacture of soap can solve the problem and eliminate lye from the home and thus save the lives of children in Hungary.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

PRESENT STATE OF CAUSTIC ALKALI POISONING. P. DUDAS, Paediat. danub. **5**:283 (April-May) 1949.

Poisoning by caustic alkali is unfortunately very frequent among Hungarian children. The number of cases has shown a constant increase in the last years. The poisoning is always followed by stricture of the esophagus. The following difficulties in feeding and the long and painful treatment exert a lasting influence on the future life of the patients.

After discussing the various pathological aspects of the poisoning, the author reviews the methods (first aid, dilatation, surgical procedures, drugs, diet) of treatment which have proved of most value during the many years of his clinical experience. Systematic treatment is the most important for the future fate of the child.

Prophylactic means, such as prohibition of the free sale of caustic alkali and penal sanctions, are urged, together with adequate education and suitable propaganda among the parents.

FROM THE AUTHOR'S SUMMARY.

Society Transactions

AMERICAN PEDIATRIC SOCIETY

Hugh McCulloch, M.D., *President*

Sixty-First Annual Meeting, Atlantic City, N. J., May 4 and 5, 1951

Experimental Production of Posttonsillectomy Bulbar Poliomyelitis. Dr. Harold K. Faber, Dr. Robert C. McNaught (by invitation), Rosalie J. Silberberg (by invitation), and Luther Dong (by invitation), San Francisco.

Characteristic features of poliomyelitis following adenotonsillectomy within a month are (1) fourfold to fivefold greater frequency of the bulbar form than in poliomyelitis without such recent operation, a statistically significant difference; (2) occurrence mainly during epidemics; (3) normal poliomyelitic incubation period after operation (with rare exception).

Previous attempts to reproduce this picture experimentally have generally failed, probably for technical reasons, though spinal poliomyelitis has more regularly been induced. Two hypotheses in explanation of bulbar localization after tonsillectomy are (1) that virus is directly introduced from the patient's throat into nerves supplying the peritonsillar muscles, thus providing a direct route of infection to the motor nuclei of the brain stem, particularly the fifth, seventh, 10th, and 12th cranial nerves; (2) that traumatic stresses increase the vulnerability of these innervating centers to damage by infection already present in the central nervous system.

In testing hypothesis 1, virus was swabbed on the pharyngeal surfaces of seven cynomolgus monkeys and the tonsils were immediately removed with curved scissors. Seven to 10 days later in all seven there developed one or more primary bulbar paralyses, referable to the following cranial nerves: fifth in two; seventh in seven; 10th in five; 12th in two. Spinal involvement, noted in three, was cervical only.

In testing hypothesis 2, six monkeys were inoculated intrathalamically and, without pharyngeal swabbing, the tonsils were removed after three days. Two days later one was found dead and five showed bulbospinal paralyses and involvement of all levels of cord; the cranial motor centers involved were third in one; fifth in two; seventh in three; 10th in five; 12th in one. Chief differences between the first and second groups were that the second showed a much shorter interval between operation and onset of symptoms and a constant and much more extensive spinal involvement.

As controls, seven monkeys were pharyngeally swabbed with virus but the tonsils were not removed. In five poliomyelitis developed eight to 10 days later; one was found dead; four had spinal paralysis, four cervical and three lumbar involvement, and one had slight dysphonia (tenth cranial), the only bulbar sign in the group.

To test the possible preventive value of local antisepsis, six monkeys were pharyngeally swabbed, first with virus, then with 2% tincture of iodine, and immediately the tonsils were removed. All six remained well.

The experiments suggest that both hypotheses are correct, but under different conditions: the first, when virus is in the throat but infection not yet established in the central nervous system; the second, when infection is already established in the central nervous system. The rarity of human cases with onset of symptoms less than four days after operation suggests that the first condition is the usual one in cases of human posttonsillectomy bulbar poliomyelitis. If so, preoperative application of an efficient antiseptic to the throat might have some preventive value against bulbar complications. This suggestion is not to be interpreted as justifying elective tonsillectomies during epidemics.

Viral Hepatitis in the Newborn: Clinical Features, Epidemiology, and Pathology. Dr. Joseph Stokes Jr., Dr. Irving J. Wolman, Dr. Mercer C. Blanchard (by invitation), and Dr. John D. Farquhar (by invitation), Philadelphia.

Evidence has been accumulating in the past decade, from such widely separated areas as the United States, England, and Australia, that infants may suffer from viral hepatitis in the first few weeks of life. In one group of 12 infants with hepatitis seen in Philadelphia the symptoms began in the first two months of life, several being born jaundiced. The pathologic findings in six of these who died were similar to those described for older children and adults with viral hepatitis, but with certain peculiar and somewhat specific morphologic changes in the liver cells. Apparently serum-hepatitis virus was transmitted to human volunteers by injection of the blood from one of the infants who died, and also of blood from his mother. In another group of 13 such infants encountered among families of men in the Army attached to Fort Benning, Ga., the father had had infectious or serum hepatitis with jaundice several years earlier, during World War II, and the hepatitis in the infants became apparent one to three weeks after birth. The clinical data and data on length of incubation period in these and several other similarly affected infants gathered from other geographic areas give strong support to the thesis that viral hepatitis, whether of the infectious-hepatitis or serum-hepatitis strains, can be transplacental in origin.

DISCUSSION

Dr. Edith Potter, Chicago: I was extremely interested in this paper because the condition described resembled one observed occasionally which is ordinarily considered congenital cirrhosis of the liver but for which there has never been an adequate explanation. Sometimes it is found in children with other malformations in whom it seems to be part of the general disturbance, but it is also seen occasionally in children who are otherwise normal, and I presume that we should anticipate the possibility that all are of viral origin.

I should like to ask Dr. Wolman whether any other characteristic findings have occurred in association with these liver changes. A few years ago in South America I saw identical changes in the liver of a child who died at 3 mo. Jaundice had been present from birth and had been originally thought due to erythroblastosis, even though no Rh antibodies were present in the blood. This child, in addition, had very remarkable bone changes. There were a generalized proliferation of bone under the cortex and a very marked osteoporosis, so that the bones could be broken in one's fingers with very little effort. We felt that there must be some relation between the changes in the bones and the liver but had no idea of the etiologic agent.

We have also seen one family in which three children died in succession, all of them under 2 yr., with similar proliferation of connective tissue in the liver and without bile-duct atresia.

The liver is an organ in which remarkable changes are found in the newborn, and this piece of work is important to call to our attention to the facts (1) that some changes may be of virus origin and (2) that not all jaundice appearing in the first day of life is caused by erythroblastosis. It has been felt so keenly that jaundice appearing in the first 12 hr. is usually due to this disease that many cases have crept into the literature as due to antibody immunization or some unknown variety of immunization for which there seems actually to be very little sound basis.

Dr. Ruth Harris (by invitation), New York: I have little more to add except that we have seen 17 patients with the identical histologic liver pattern and five other patients with the same clinical course. Most of these patients had erythroblastosis caused by Rh or blood-group incompatibility. While almost all had transfusions at birth, liver disease from serum hepatitis seems improbable because the disease antedated transfusion. One patient with a case of mild Rh disease had a pyloromyotomy and liver biopsy at the age of 1 mo. These liver sections appeared similar to those described by Dr. Wolman.

One erythroblastotic infant with jaundice for four months and typical results of liver biopsy was tested at the age of 2 yr. with an apparently potent supply of the hepatitis antigen of Dr. Stokes. The skin reaction was negative. Of course, this one case does not disprove the possibility of infectious hepatitis as the cause of the liver insufficiency, but it suggests that more than one etiologic factor may exist. Bacterial infections may produce a similar picture. One of our patients with this liver pattern had a coincidental bacterial urinary-tract infection.

DR. CHARLES A. JANEWAY, Boston: I am indebted to Dr. Stokes and Dr. Wolman and their group for this excellent work. A few years ago Dr. Wolfe and I tried to get at this problem by epidemiological means during a severe epidemic of infectious hepatitis in the community, when admissions for hepatitis were very high. We could trace the epidemics over a 15-yr. period by charting the admissions for hepatitis from our records. The thing that was striking was that instances of acute yellow atrophy were scattered all along the chart and not grouped after the epidemics of acute infectious hepatitis, as might have been expected. This suggests that cases of infantile and childhood cirrhosis of the liver may have been due to the virus of serum hepatitis rather than that of epidemic hepatitis.

In infants the problem of hepatitis is very interesting when you begin to consider what is known about the viruses. The virus of serum hepatitis, from Dr. Stokes' work, may be found in the blood of a certain number of normal persons who are essentially carriers. Many of these carriers show very minor abnormalities of hepatic function, but a striking fact is that donors who have caused serum hepatitis in recipients of their blood are very often people who have no clinical history of jaundice whatsoever. It is easy to see how pregnancy in a person who is a carrier of the virus might lead, if the virus passes the placenta, to infection in the baby. If that is true, the short incubation period from birth to onset of jaundice in Dr. Wolman's cases indicates that the virus probably crossed the placenta well before the baby was born.

As to the question of whether or not infectious hepatitis occurs in the baby by transplacental transmission, the facts about the infectious-hepatits virus are against it. The virus is in the blood stream of the patient only at the time when he is acutely ill with prodromal symptoms of infectious hepatitis, which are followed very shortly by the development of antibodies. Consequently, it seems unlikely that a baby can get infectious hepatitis by transplacental transmission unless the mother contracts the disease at the very termination of pregnancy. If she contracts it within a few weeks before the end of pregnancy, or earlier, and the virus should cross the placenta, in all probability antibodies would cross the placenta before the baby is born and protect the baby in exactly the same manner as gamma globulin will prevent the the disease in susceptible persons when administered before they succumb to the disease.

It will be very interesting if Dr. Stokes' group can work out whether or not the viruses in these babies all have the characteristics of the serum-hepatitis virus, as seems to be the case in the few inoculation experiments shown here.

Biopsy is likely to be a hazardous procedure in these children who have cirrhosis and hepatitis. We have had bad experiences in subjecting patients to laparotomy and biopsy of the liver in the face of severe liver damage.

DR. DOROTHY H. ANDERSEN, New York: We have been interested for several years in the same liver changes. Several years ago I analyzed all of our surgical and postmortem material in which lesions of the liver had been diagnosed during infancy. By selecting those cases in which multinucleated liver cells containing pigment were a prominent feature, we arrived at a group of 12 cases. On investigation of the charts of these cases it was found that three with more extreme liver changes were cases of acquired hemolytic anemia, six were cases of Rh disease, and three were undiagnosed. In one of the latter cases the patient was an infant both of whose parents had had hepatitis the year prior to his birth. From these observations I came to feel that the reaction of the liver by the formation of multinucleated cells was not characteristic of one disease but was rather a characteristic of the liver response to a variety of stimuli in infancy. This opinion is reenforced by the fact that neither hemolytic anemia nor hepatitis in the adult produces this picture.

The report of Dr. Stokes and Dr. Wolman has made clear some of the mysteries and added some more, as is usual in productive work.

I should like to say that our experience with biopsies has not been as gloomy as the experience in Boston apparently has been. A large proportion of the material has been collected by way of biopsy in the course of surgery.

Some of these liver biopsies were done during exploration of jaundiced infants thought to have atresia of the bile ducts. Some of these patients were considered inoperable and later recovered spontaneously. In retrospect, it seems probable that the existence of this type of hepatitis may provide an explanation for the reported cases of spontaneous recovery from atresia of the bile ducts.

DR. WOLF W. ZUELZER, Detroit: The importance of the work of Dr. Wolman and his associates is evident. In the past it has been almost axiomatic that viral hepatitis does not occur in infants under the age of 2 yr. Therefore, I would like to add a word about the experience we had in Detroit over a number of years with cases in which the autopsy presented a picture identical with that described by Dr. Wolman. In passing, I want to stress what the other discussants have already said and what Dr. Wolman himself pointed out, namely, that the morphologic picture is probably not specific.

About the same time that the peak of the cases in Philadelphia was observed (around 1948-1949), there was an epidemic of what was called diarrhea in the premature nursery at the Children's Hospital of Michigan. In approximately 50% of the infants icterus developed, and there were additional disturbances, as shown by liver-function tests. Approximately 50% of those infants who became icteric and had an enlarged liver died and were studied at autopsy. The findings were the same as Dr. Wolman's.

These infants came from homes and different hospitals but had been in one and the same nursery before their illness developed. They were all premature infants. Most of them had received blood and plasma transfusions but not from a pool or from the same blood. The development of the illness in such a group does not indicate transplacental origin. The epidemiological features would point to a viral origin of the disease. The question in our mind was whether this was a peculiar diarrhea virus complicated by hepatitis or the virus of infectious hepatitis producing the symptom of diarrhea in this particular type of patient.

The morphologic changes of homologous serum jaundice or adult-type infectious hepatitis in infants, however, may be identical with that seen in adults. We have had one or two experiences with infants who died with what we labeled homologous serum jaundice, and the microscopic picture of the liver was very much like that described in adults. Therefore, the etiologic factor of the condition described by Dr. Wolman and perhaps also of our own cases may well be still a different virus from that of adult serum hepatitis.

DR. MITCHELL I. RUBIN, Buffalo: I am sure it is surprising to everybody that I should arise to discuss a subject dealing with patients who do not have renal disease.

I should like to ask Dr. Wolman a question. We had two children in the last three months who have come from the same area, just outside of Buffalo, for whom a diagnosis of hepatitis was made. They were jaundiced at birth. One of them finally died with cirrhosis of the liver at the age of 3 mo. The other child with apparently the same condition is recovering.

The peculiar thing about these children is that for both erythroblastosis fetalis was diagnosed because of the large number of nucleated red cells present in the blood. There was no evidence of sensitization by either the A-B-O or Rh antigens in these patients. Yet, because of the clinical appearance of one of these patients, an exchange transfusion was performed. An incorrect diagnosis of erythroblastosis was made. I wonder if Dr. Wolman found large numbers of nucleated red cells in the blood of his patients with hepatitis.

DR. IRVING J. WOLMAN, Philadelphia: I should like to thank the discussants. I believe they have raised more questions than we can answer.

With reference to Dr. Potter's question, there were no anomalies in any of our patients. There was no family history of other babies' being born with jaundice.

Reference was made to the skin-test antigen for hepatitis. That skin-test antigen is still under development. The batches thus far have been of uneven potency and not too reliable; consequently, a negative reaction would not rule out hepatitis.

The question of erythroblastosis has been hinted at by several of the discussors. It is not impossible that a liver lesion of the type we have described can be an atypical reaction to a blood-group incompatibility. If that is so, we must reexamine and expand our present conceptions of erythroblastosis fetalis.

I did not mean to give the impression that the multinucleated liver cell is a specific cell reaction to hepatitis. That must wait for the accumulation of more data. We have seen occasional large cells of the type described in livers of children dying of other causes when liver disease was not prominent, but a large preponderance of cells of this type does raise the question.

We agree with Dr. Janeway that these babies probably had serum-hepatitis virus rather than infectious-hepatitis virus, but we can not talk with certainty on that, except in regard to the one case in which the study with use of volunteers was made. It is true that hepatitis is

latent in our population. It is true also that at least half of the adults with hepatitis do not have jaundice—and the same is probably equally true for infants. The patients discussed were selected because they had jaundice. It is very likely that many babies do have hepatitis without jaundice. It has been suggested by other evidence not given here that epidemic diarrhea of the newborn may at times be caused by a virus similar to that of epidemic hepatitis. For example, in some outbreaks of epidemic diarrhea some of the babies have had jaundice.

Adult hepatitis at biopsy or at autopsy is very different from what has been shown here. Dr. Mallory and Dr. Luicke have examined these sections and have said they have not seen any lesion of this kind in any adult. We have also seen, as Dr. Zuelzer brought out, other infants with what seemed to be hepatitis who had lesion of the liver more similar to what is familiarly recognized as being hepatitis in the adult. Whether the cellular changes described represent a variant of hepatitis or some other kind of virus disease or are instead a nonspecific response of the liver cell to injury is still uncertain.

None of our babies came to attention until they were 1 or 2 weeks of age. At that time they did not have nucleated red cells in any quantity in the circulation or any other changes in the peripheral blood that were peculiar.

Later Results of Measles Encephalitis. Dr. Edith Meyer (by invitation) and Dr. Randolph K. Byers, Boston.

A follow-up investigation as to the course and outcome of 16 cases of measles encephalitis occurring between 1943 and 1949 was made. The children were studied at intervals of months or years, and the total follow-up period varied from seven months to seven years, with 11 being followed for three years or more.

Under investigation were, first, the developmental progress of the children after the acute phase of the disease; second, the question of whether the term postencephalitic behavior could be broken down into more understandable concepts than those at present current; third, the possibility of developing a plan which might minimize the usually resulting maladaptation; fourth, the description of various stages in the recovery process in psychologically diagnostic terms, and, finally, the influence of age at onset on the psychological changes and behavior patterns. In addition to the usual quantitative intelligence scales, a group of 26 tests of learning, attention, drawing (copying and memory), word learning, and picture completion were used to show qualitative aberration of psychological function.

At onset, the ages of the children varied from 22 mo. to 10½ yr. Neurologic symptoms appeared as early as the day of the rash and as late as 13 days after the rash. In one child vaccinia and measles occurred together, and either or both could have been etiologic. In all instances clinical evidence of involvement of the cortex occurred, and in 10 myelitis was also found, and blindness occurred in four.

The total group was rather readily divided according to acute attacks into a group with a short course of days or a few weeks and a group with a prolonged course. The seven children in the first group were usually discharged after a few days or weeks of hospitalization as socially functional individuals. The nine children with prolonged acute courses showed obvious impairment of independence on discharge weeks or months after onset.

In the first group adequate psychological recovery occurred in all patients save one, whose illness began within six months of the follow-up study. In most of these children attention defects, easy intellectual fatigue, and impaired learning ability characterized their psychological status for periods up to a year, though quantitative intelligence tests showed normal results. After that, all save one showed considerably better performance than verbal ability, though all, as judged by the Wechsler Intelligence Scale for Children, fell in the normal range. All save the most recent patients were competitive individuals.

As a group, the nine children with the more prolonged acute illness did not recover as well. In the seven examined at the time of discharge, the results of quantitative psychological tests were adequate because of the children's ability to mobilize their previously acquired stock of information. Restlessness, fatigability, and short attention spans were prominent disabilities. As the children became more durable, more thorough examinations showed persistence of the

attention defect, loss of learning ability, inability to distinguish between details and main theme, inability to memorize abstract designs, and confusion of background and figure. Of these, the attention defect seemed the most fundamental.

When these defects persisted over a period of years, the IQ showed a gradual decline, but it was often years before the IQ gave an adequate estimate of the disability of a child with severe psychological damage.

Behavior problems seemed clearly related to the impact of the environment on psychologically damaged personalities. In the cases with short acute courses, change in psychological durability and competence were so apparent to the parents that behavior problems were usually relatively easily managed on a "hold the fort" basis. In the severer cases, stupid or emotionally disturbed parents were usually unable to understand the child's needs. Rigid or intolerant school systems sometimes added to the difficulty; when it was possible for parents to accept the children's limitations and for the schools to supply a kindly home teacher or to allow repetition of grades without disgrace to the child, behavior problems did not become important.

Age at onset seemed to have a bearing on total outcome. Older children appeared to be able to function competitively in spite of psychological impairment of a degree which rendered younger children incompetent. This seemed to be the result of a previously acquired stock of information and working habits in the older children, whereas the younger children were unable to acquire these basic adaptations in the face of perceptual difficulties.

The psychological outcome seemed totally unrelated to methods of care.

DISCUSSION

DR. HONOR SMITH, Oxford, England: I have had very little experience with measles encephalitis, but I was most interested in Dr. Byers' paper. There is one point I should like to ask him. He mentioned the myelitic component, and, in the few cases that I have seen, the myelitic component has always been a very large one. I should like very much to know whether there is any evidence of residual cord damage or if the cord appears, so far as he can tell, to have a very complete recovery. I should like, for instance, to know whether there is a residual extensive Babinski reflex or anything that can be picked up in detailed examination which might be analogous to the behavior disorders of the cerebellum which presumably result from cerebral damage.

DR. HORACE L. HODES, Baltimore: Dr. Livingston and I had an experience with electroencephalographic changes in eight children with measles encephalitis. We came to a slightly different conclusion from that expressed by Dr. Byers. We found that in all instances the electroencephalographic changes persisted after the children became clinically quite well, but we did think that the encephalogram was of some prognostic value. In the seven children who recovered, the electroencephalogram became normal. In the one child who did not recover, the electroencephalographic pattern remained quite abnormal.

Among the children who did recover, it took as long as eight months for the electroencephalogram to show normal results. Incidentally, children with measles who did not have central nervous system signs did not exhibit abnormal electroencephalographic patterns.

DR. PHILLIP E. ROTHMAN, Los Angeles: In a disease such as measles encephalitis in which spontaneous recovery occurs not infrequently, it becomes very difficult to evaluate any therapeutic agent during the acute stage. Drs. Hodes and Livingston's report that the clinical recovery precedes the return of the electroencephalogram to normal makes me wonder if a more rapid return would indicate the effectiveness of a therapeutic agent.

We have recently seen a case in which treatment with cortisone gave rather striking results during the first week. I wonder if Dr. Byers would comment on the use of it and the possibility that a rapid return to normal of the electroencephalogram would mean that the agent is effective.

DR. SAMUEL KARELITZ, New York: I wonder if Dr. Byers would tell us whether the child who received gamma globulin six or seven days before the rash actually had modified measles. The incidence of encephalitis in modified measles is still very, very low.

DR. RANDOLPH K. BYERS, Boston: In reply to Dr. Honor Smith, the children with myelitis recovered very slowly in most instances from the myelitis. Of the 10 who had definite cord symptoms, one child, on whom we now have a follow-up period of six years, has a good deal of difficulty with bladder function. She has to carry an alarm clock around with her and wake herself up at night and go to the bathroom at intervals of about three hours. She has to go to the bathroom during the day by the clock because she is unaware of when she has to empty her bladder. She had pyramidal-tract signs such as Babinski's for two and one-half to three years after the acute phase. Now six years later, so far as functioning of the legs is concerned, she is doing very well. She comes in now and describes her improvement in terms of the latest mountain she can climb rather than any degrees lesser than that.

Another child also has severe sphincter disturbance, with loss of both bowel and bladder control, and some leg weakness. In the remainder of the children symptoms have cleared up completely, so far as I can tell.

With reference to Dr. Livingston's and Dr. Hodes' observations, we have not been able to get any very good correlation with our electroencephalograms. Some of the children who have done very well have had spikes persist in their electroencephalograms for four, five, and six years after the acute attack. One child who makes no sense at all has a completely normal electroencephalogram, so far as I can see, and I must say that the worst electroencephalogram we had was of the child who had done the worst of all.

I have had no experience, of course, with the treatment of this disease with cortisone. These children were all seen before cortisone came on the map, and we haven't worked with any since. One or two of these children recovered remarkably quickly from the acute disease. Convulsions, confusion, and coma developed, and, so far as the gross symptoms of that sort were concerned, the children were recovered in three or four days and discharged from the hospital in a week or 10 days; so rapid recovery without cortisone can occur.

In answer to Dr. Karelitz' question about the gamma globulin, I am speaking now from memory because I haven't all the case histories with me, but the child who received the gamma globulin had only a moderately modified attack of measles. Her temperature during the disease, as I remember it, ranged around 102 or 102.5 F., and she had a relatively acute rash which was certainly not more modified than that in some of the cases of mild disease we used to see before the days of gamma globulin.

Immunization in the Young Infant. DR. J. CYRIL PETERSON (by invitation) and DR. AMOS CHRISTIE, Nashville, Tenn.

This paper was published in three parts in the April, 1951, issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, pages 483, 501, and 519.

DISCUSSION

DR. PAUL A. DI SANT' AGNESE (by invitation), New York: Some time ago we had an opportunity to study the production of antibodies in response to an antigenic stimulus in a group of young infants. We had essentially the same results as those just reported by Dr. Christie and reached conclusions only slightly at variance with his.

The main difference between the two studies was in the age of the infants; all our newborn infants were 7 days of age at the time of first injection. The results of antibody production in these newborn infants were compared with the results achieved in a group of older children who had the same antigens in the same dosage and on the same schedule. We concluded at that time that age does influence adversely the production of antibodies in young infants, but that the handicap due to immaturity of the immune mechanisms could be overcome by increasing appropriately the antigenic stimulation, and that, therefore, routine immunization against whooping cough, diphtheria, and tetanus could be undertaken at an early age with assurance of success in a majority of cases.

One other factor mentioned by Dr. Christie needs to be reemphasized, and that is the importance of booster doses in consolidating the immunologic gains achieved by primary or basic immunization. This is important in protection against not only diphtheria but also tetanus and whooping cough.

Tetanus in children is frequently due to wounds so small as to be overlooked. It is important, therefore, that circulating tetanus antitoxin be kept at levels which afford protection at all times. This can be achieved, of course, only by repeated booster doses.

The same thing is true of whooping cough immunization. In New York, it has become increasingly the practice not to give booster doses, and it does not seem logical to me to give a basic course of immunization against whooping cough without following it with at least one booster dose to tide children over the first two years of life, in which the disease has to be feared most.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: I think every one who has worked with Hemophilus pertussis as an antigen will agree that it is a relatively weak one, for so many organisms are required to accomplish the desired degree of antigenic stimulation.

An interesting, but perhaps important, fact is that pertussis vaccine when injected in combination with diphtheria toxoid enhances the antigenic properties of the latter. This may be of some practical value when combined antigens are injected in the early weeks of life, an age when the question of the effectiveness of active immunization against diphtheria may arise. However, from experiments on rabbits we observed that diphtheria toxoid mixed with pertussis vaccine did not significantly increase the agglutinative titer of the blood against H. pertussis.

DR. WILLIAM C. DEAMER, San Francisco: Would Dr. Christie comment on the response to the recall injection of those infants whose response to basic immunization was the poorest? In an investigation similar to his that we made several years ago, we studied tetanus antitoxin responses and were struck by the great variation in the amount of antitoxin formed by infants of the same age. As Dr. Crothers implied earlier, the result was not entirely uniform, despite the uniform procedure used, and we encountered variations of several hundredfold in the amount of tetanus antitoxin achieved.

Since we presumably have to gear the program to the poorest responders, information about them is of interest, as in practice we seldom have follow-up titer studies such as have been reported.

One other thing of interest to us was apparently not experienced by Dr. Christie; namely, the observation that the poorest initial responders—that is, those who achieved poor levels on basic immunization—often achieved good, and sometimes outstanding, levels on recall injection. There was perhaps some association of poor initial response and poor recall response. I know the poorest initial responder turned out to be the poorest recall responder; but, in general, the correlation was poor.

DR. A. ASHLEY WEECH, Cincinnati: Dr. Deamer has asked essentially the same question that I want to ask. Since the percentiles and quartiles, as well as all techniques of statistical compilations, are particularly effective in masking the path traveled by the individual person, is there a correlation between the degree of primary response to immunization and the response to recall injection later on?

In studies with which I was associated during World War II on the response of young men of army age to toxoid immunization against Clostridium perfringens, a large group who had been immunized with a type of toxoid which was considered completely inadequate during the period of primary immunization, subsequently, as an afterthought, was retested after a booster injection of toxoid. Their response, measured in terms of the height of antitoxin levels, was the best that we observed in the entire group.

This experience has made me feel that in studies of immunization of this type the primary stress should be placed on the levels of antitoxin achieved after immunization is complete, and by that I mean both the primary immunization and the recall injection given between six months and a year and a half later.

DR. AIMS C. MCGUINNESS, Philadelphia: We have had a great deal of experience with the pertussis immunization of adults, and it is our feeling that each person has his own antibody ceiling. Ten per cent, roughly, of the nearly 1,000 adults whom we have immunized in the preparation of hyperimmune serum failed to achieve agglutination titers greater than 1:320. We have endeavored to increase these titers by giving large doses of vaccine. Several persons have received as much as 100 cc. of vaccine in a year, and even with these huge doses we were

unable to achieve titers more than one, or at most two, tubes above the levels attained after the usual 8 cc. course of vaccine administration, and the levels still remained well below the minimum required titer of 1 : 1,280.

On the basis of this experience it would seem safe to assume that perhaps 10% of children inherently are unable to achieve satisfactory levels after immunization. Emphasis should be placed on improving pertussis antigens rather than on increasing the amount of antigen in our vaccines. Vaccines containing organisms in concentrations above 15 to 20 billions per cubic centimeter cause increasingly severe reactions without materially increasing the antibody response.

DR. CHARLES HENDEE SMITH, New York: We have heard discouraging reports on the effect of diphtheria toxoid, but diphtheria is almost stamped out. In a community in which I have worked for the last nine years, there has been only one small epidemic of diphtheria and that was among children in a parochial school which at that time did not require diphtheria immunization. No child in the community who had had any immunization, with or without booster injections, acquired diphtheria.

The story with tetanus is much the same. We see no tetanus. However, whooping cough is still far from being controlled. Children who have been given injections (with or without booster injections) of whooping cough antigen continue to get whooping cough. It is most discouraging to the practitioner to immunize children, especially if the whooping cough antigen gives severe local or general reactions, when within a few years they have whooping cough. More emphasis and effort should be placed on work in that direction than on a study of the apparently poor results from the serological titer of diphtheria.

DR. BÉLA SCHICK, New York: The questions being raised today have troubled us for many years. The study of Dr. Peterson and Dr. Christie was made on a large number of infants. Whether or not a child possessing antibodies against diphtheria toxin can be actively immunized with diphtheria toxin or toxoid is very important. This possibility is frequently denied. The only difficulty in accepting such a verdict lies in the fact that the manufacture of highly potent diphtheria antitoxin is accomplished by repeated injections of diphtheria toxin or toxoid into horses which have antitoxin in their serum as a consequence of previous injections. Of course, the dose of toxoid or toxin is steadily increased. It is furthermore interesting that horses which have some preformed antitoxin present in their serum are better producers of highly potent antitoxin than horses which have no antitoxin in their serum when the immunization is started.

Adults should be immunized with subneutralized toxin-antitoxin mixtures with the knowledge that the mixture will be dissociated in the organism.

The ability to produce antitoxin varies individually. This difference may be less conspicuous or not present after the second and third injections.

I expressed the idea that the difference in the severity of clinical diphtheria is due to the individual differences in the rapidity with which antitoxin is produced. The appearance of antitoxin is not interfered with by the therapeutic injection of diphtheria antitoxin.

DR. CLEMENT A. SMITH, Boston: I want to add, in the interest of accuracy, that, as Dr. Warren Wheeler pointed out to me some time ago, one has great difficulty in comparing the antibody production of newborn infants with that of older infants when one uses depot antigens. These are antigens which remain localized for some time, so that, although they are introduced in the newborn period, they remain at work for several weeks or months thereafter. Therefore, strict conclusions of a theoretical nature concerning the power of the newborn infant to form antibodies cannot be drawn from such work, important as it is from a practical standpoint.

DR. MYRON E. WEGMAN, New Orleans: While it is highly desirable in an individual child to raise the level of immunity to its highest point, in the long run, protection of the individual child also depends on general community protection. Consideration of a desirable immunization schedule, therefore, involves how many children, that is, what proportion of the community's children, will be available for immunization. All studies in child-health centers indicate that attendance falls off from the first and second month on. There is probably a similar situation in physicians' offices, meaning that the later immunization is begun the fewer children will be reached. This, to me, forms a strong argument in favor of Dr. Christie's thesis that, if one starts early, one accomplishes more.

DR. WILLIAM A. REILLY, Little Rock, Ark.: What does Dr. Christie consider a favorable protective level of antitoxin? I have seen 13 patients with toxic diphtheria, each having a negative Schick reaction.

DR. AMOS CHRISTIE, Nashville, Tenn.: I should like to say to Dr. di Sant' Agnese that we have some clinical and laboratory evidence to support the idea that the higher the flocculating unitage of the material that we are using, the better the antigenic responses. There is a marked variation among many of the commercially available materials.

In answer to several of the discussants, a large amount of individual variation is apparent on study of the the material case by case or infant by infant. On the other hand, the overwhelming majority of the cases follow one pattern or another. We debated this for some months in an attempt to know how best to present this material, whether to show it with scattergraphs, as in Dr. Deamer's earlier studies, or to show individual patterns representing a few typical cases with various types of responses. Finally realizing, as Dr. Weech pointed out, some of the limitations of the quartile method, we concluded that this perhaps would best illustrate the points which we wanted to make. Dr. Boyd's pioneer use of this method of illustrating individual variations in growth material encouraged us. We were not so much interested in the evaluation of an antigen as in studying the factors responsible for the individual variation, as well as those responsible for some children's failing to respond as well as many others.

About 75% of the children at Vanderbilt University who have been admitted because of tetanus are in the group under 15 yr. of age. Perhaps that can be used as an argument for the inclusion of tetanus in this antigen mixture. Incidentally, 50% of those children had no history of puncture wound or portal of entry; thus, tetanus is a relatively silent disease and is liable to come up at any time—another reason for routine tetanus immunization.

Yes, Dr. Bradford, we have some evidence to show that the addition of pertussis antigen to the diphtheria and tetanus antigen mixture improves the titers of all. I hoped someone would say sometime during the presentation that, while more organisms per dose may be the answer, the improvement of the antigen in other ways in order to get better immunization titers, as well as more prolonged protecting levels, is an important aspect of any future studies.

Susceptibility of Hemophilus Parapertussis to Certain Antibiotics. DR. WILLIAM L. BRADFORD and ELIZABETH DAY (by invitation), Rochester, N. Y.

The in vitro susceptibility of Hemophilus parapertussis to a number of antibiotics was determined. Twelve strains of the organism, previously lyophilized soon after isolation, were tested. Various twofold dilutions of each antibiotic were incorporated into Bordet-Gengou medium. Uniform amounts of a standard suspension of the organism were spread upon the surface of the medium. After incubation at 37 C. the degree of growth inhibition was observed at the end of 48 and 72 hr. The results were recorded according to the highest dilution resulting in no growth, and the 50% end point was calculated.

The antibiotics tested, in order of greatest susceptibility as determined by this method, were aerosporin® (polymyxin B), terramycin, chloramphenicol (chloromycetin®), aureomycin, neomycin, streptomycin, and penicillin.

The in vivo susceptibility was determined by observing the therapeutic effect of five daily intra-abdominal injections of various dilutions of the antibiotics against the standard experimental infections in young mice. Ten mice were used for each dilution of the drug tested. The number of mice surviving at the end of five days was observed, and the dose of antibiotic in milligrams per kilogram of body weight a day which protected 50% of the mice was calculated.

According to this method of testing, aerosporin® (polymyxin B), aureomycin, and terramycin gave the best results.

Comparison of the antibiotic spectrum of H. parapertussis was made with that of H. pertussis.

Comparison of the Therapeutic Efficacy of Four Agents in Whooping Cough. DR. R. G. AMES (by invitation), DR. S. COHEN (by invitation), DR. A. E. FISCHER (by invitation), DR. J. KOHN, DR. A. Z. MCPHERSON (by invitation), DR. J. MARLOW (by invitation), DR. J. RUTZKY (by invitation), and DR. H. E. ALEXANDER, New York.

This paper presents the results of a study designed to compare the therapeutic efficacy of four different therapeutic agents, streptomycin, chloramphenicol (chloromycetin®), specific rabbit

Hemophilus pertussis antiserum and human hyperimmune serum, with the efficacy of supportive treatment in a control group. Two hundred and sixty-five patients were studied—approximately 50 under each therapeutic regimen. One-half were 6 mo. of age or less and one-fourth 3 mo. or younger.

A resident was assigned to the pertussis ward full time, a well-trained pediatric clinician assessed the result of treatment in each patient in the study four times weekly, and a bacteriologist trained in the isolation of H. pertussis devoted full time to this study.

In order to avoid bias, the treatment for each patient as well as the selection of those to serve as controls was chosen by a lottery method. To minimize the variable influence of secondary bacterial invaders, slowly absorbed penicillin was given to all patients intramuscularly once daily for five days when therapy was begun, or after 48 hr. in controls.

Change in the course of the disease was judged on the basis of the following criteria: character of paroxysms, food intake, vomiting, respiratory rate, amount of mucus, weight, and white blood cells; data on these were recorded daily. At 6, 10, and 21 days after the beginning of specific treatment, or observation in the controls, the result was listed as a success if there was improvement in five of the seven criteria; the scoring demanded that improvement in the character of the paroxysms be one of the five. From analysis of the data certain facts are clear: 1. The control patients who received penicillin to eliminate the majority of secondary invaders exhibited a mild disease. Only three were deemed to require additional treatment. 2. Not one of the specific therapeutic agents was followed consistently by prompt subsidence of the signs of whooping cough.

The three factors which influence results of any treatment, age, severity of infection, and duration of cough, were well distributed among the therapeutic groups and controls, with the exception of the human-serum-treated group, in which there was a smaller percentage of patients with mild infections and a larger proportion of infants under 3 mo. of age.

The analysis concerned with comparison of therapeutic efficacy of the four therapeutic agents is in progress.

DISCUSSION

DR. HATTIE ALEXANDER, New York: First, I should like to discuss Dr. Bradford's paper. Our in vitro examination (*J. Clin. Invest.* **28**:867, 1949) of the action of streptomycin on H. pertussis and H. parapertussis has yielded results quite similar to those just shown by Dr. Bradford. There is every reason to anticipate therapeutic failure of streptomycin in H. parapertussis infection, but we have had no experience with the in vivo action.

Since streptomycin has been reported by some to be effective in whooping cough caused by H. pertussis, and since it is not possible to distinguish clinically from H. parapertussis infections, Dr. Bradford's results deserve special emphasis. An occasional severe H. parapertussis infection is seen and requires the most effective treatment available. Since all three of the newer antibiotics, aureomycin, chloramphenicol, and terramycin, have been shown to be bactericidal, the choice would be made on the basis of tolerability.

Our selection of chloramphenicol rather than aureomycin at the time we started our study was based not on demonstration of a superior antibacterial effect in vitro, that is, so far as prevention of growth of the organisms was concerned.

While both aureomycin and chloramphenicol were shown to be bactericidal, chloramphenicol exhibited greater speed of lethal action; terramycin tested later was found equal to chloramphenicol in rapidity of bactericidal action.

We were also influenced in our choice between the two antibiotics by the greater tolerability of the gastrointestinal tract for chloramphenicol.

DR. LEWIS L. CORIELL (by invitation), Philadelphia: I should like to comment on Dr. Ames' paper and give our experience in treating 85 patients with whooping cough at Camden Municipal Hospital. Our observations were closely parallel to the data presented here. In our area patients are not sent to the hospital with normal whooping cough, which has been here described as a mild disease. The average duration of whooping before admission in our series was 12 days. A very good percentage of these patients were seriously ill, with presenting symptoms of cyanosis, fever, vomiting, dehydration, or convulsions.

The criteria for evaluating the therapeutic effect of antibiotics were those used by Dr. Ames and her group, except that we chose a four-day period rather than six days. Since the introduction of sulfonamides and penicillin few children die of whooping cough, and consequently death cannot be used as a yardstick in measuring the efficacy of the newer antibiotics. Less reliable clinical signs must be used.

By our clinical criteria 75% of the penicillin-treated patients failed to show significant improvement within four days. Those treated with aureomycin, chloramphenicol, and streptomycin showed 45, 40, and 66% failure respectively. Forty per cent of the patients treated with hyperimmune human serum failed to show significant improvement within four days. However, the most critically ill patients received serum. Ninety-five per cent of the patients hospitalized had not been immunized.

We are particularly impressed with the value for the severely ill patients of supportive measures rather than "specific" therapy, so far as lifesaving and rapid recovery are concerned. All the controls received penicillin, and we could not withhold oxygen therapy, intravenous feeding, and sedation when indicated. In managing the severely ill, convulsing patients, we are most impressed with the value of intravenous thiopental (pentothal®) sodium and intramuscular phenobarbital sodium to suppress the cough, convulsions, and resultant cerebral damage from cyanosis and interference with respiration.

Dr. Jerome L. Kohn, New York: Commenting on Dr. Bradford's paper, it would appear that parapertussis is not an important diagnostic problem at the Willard Parker Hospital. Over a period of years H. parapertussis was cultured only occasionally. It is easier to culture H. parapertussis than H. pertussis from the nasopharynx. In the material of the present report on the use of various therapeutic agents in whooping cough, H. parapertussis was found only once.

Commenting on the whooping cough study, it was decided at the start of the investigation that two sets of clinical observations be made independently. None of us had any knowledge of the therapeutic agent, if any, given to the individual patient. The results obtained by using the seven criteria were later compared. In arriving at the clinical estimate of each patient, obviously most of the criteria were included. Therefore agreement was usually obtained. It should be noted that the clinicians who made the independent observations were experienced in the care of children ill with whooping cough. Critical clinical observation has its place in estimating the apparent response of any therapeutic agent in a disease with such a varied picture as whooping cough.

Comparing the methods, there was general agreement in evaluating the severity of illness as well as in response to therapy in about 85% of the patients. This demonstrated the value of certain criteria as an objective method. It appeared that the criteria which were employed had a tendency to make the estimate of illness, as compared with clinical impressions, somewhat milder in some instances.

As for the criteria themselves, if a similar study were made again, we would probably modify the scoring of the criteria. For example, the character of the blood count did not appear to have much significance.

As Dr. Ames said, the routine use of penicillin surely reduced the incidence of secondary infection in these young children. Therefore, on the whole the clinical course became milder.

Dr. Ames, because of lack of time, took it for granted that it was understood that all these children received the basic treatment. When indicated, oxygen therapy, aspiration of the upper respiratory tract, hydration and use of parenteral therapy, special feeding technique, and special nursing care were employed.

I should like to ask Dr. Ames if she would tell us something about the persistence of H. pertussis in the nasopharynx while the various therapeutic agents were employed.

Dr. Herbert C. Miller, Kansas City, Kan.: I surmise that one of the difficulties in evaluating whooping cough in a large group of infants from newborn to 3 mo. might be related to the fact that nobody knows when the cough reflex is established in this age group. We have been interested in this problem and have not gone very far with it at the present time, but one of our babies at 55 days of age still did not exhibit any cough reflex, and I think that until we know more about the establishment of the cough reflex in these babies, the evaluation of the cough in whooping cough will continue to give considerable difficulty.

DR. WILLIAM L. BRADFORD, Rochester, N. Y.: I thank the various discussants, although most of their remarks concerned the other paper!

Dr. Alexander stressed an important point when she observed that the control group in Dr. Ames's experiments was actually a treated group. Penicillin, no doubt, protected this group against the common secondary invading organisms. Moreover, there is evidence that penicillin is also effective, in higher concentrations, against H. pertussis itself. However, one should not question the humaneness and wisdom of using it in this type of clinical investigation, even though it changes the nature of the experiment in much the same way that one modifies the regular game of football into "touch" football in order to eliminate some of its risks.

Dr. Kohn's statement that he has not observed H. parapertussis in New York somewhat surprises me, for I can't imagine this great city, possessed of so many interesting things, being without this organism! We continue to isolate it, from time to time, in Rochester, but not with the frequency we found in 1937 when we first observed it. At that time we encountered it in 5% of the total cultures positive for H. pertussis. At the Serum Institute in Copenhagen Dr. Latrop is now observing that 20% of the total positive cultures taken for H. pertussis are H. parapertussis, a finding which confirms the fact that the two diseases can be differentiated only by bacteriological methods.

Dr. Miller's reference to the delayed development of the cough reflex in certain very young infants is appropriate, for it may explain the tendency of the subject at this age to choke rather than exhibit a typical paroxysm.

DR. HATTIE ALEXANDER, New York: There are a couple of direct questions which I should answer. Dr. Kohn asked me to say something about the persistence of H. pertussis in the various therapeutic groups. It was summarized earlier, but perhaps he wants figures. I think it is important to state that the figures that I am going to give are based on culture of four samples of nasopharyngeal mucus whenever culture was done. In the control group 50% showed cultures positive for H. pertussis seven days after the beginning of therapy. The group treated with streptomycin and with human antiserum showed no difference from the controls. In the rabbit-antiserum-treated group only 11% of the patients still showed positive cultures seven days after the beginning of treatment, and of those treated with chloramphenicol about 27% still showed positive cultures at seven days.

Our experience with the action of penicillin on H. pertussis has not shown it to be as effective as was reported by Dr. Bradford. For example, most groups in the country now are incorporating penicillin in the Bordet-Gengou medium for initial isolation of H. pertussis in order to inhibit gram-positive cocci, and we find that 0.2 to 0.5 of a unit per cubic centimeter of medium is the range which is effective in inhibiting these organisms without inhibiting H. pertussis. About 90% of the patients who were admitted with the clinical diagnosis of whooping cough showed H. pertussis in the nasopharynx when culture was by this method. Therefore, I don't believe we were inhibiting many H. pertussis organisms with 0.5 of a unit per cubic centimeter. We find it is possible regularly to eliminate H. pertussis with a level of about two units per cubic centimeter, but the dosage used clinically would never attain those levels in the body fluids.

I would just like to make one other statement, namely, that H. parapertussis does occur up about 168th and Broadway. One summer we isolated six or seven strains in the course of two or three months. Since that time we have encountered fewer strains; during the period of this study they were rarely seen.

Protean Manifestations of Salmonella Infection in Infancy and Childhood. DR. ISAAC F. GITTLEMAN (by invitation) and DR. JOSEPH B. PINCUS (by invitation), Brooklyn.

This study is based on clinical, pathological, and serological observations which we made on a series of 17 children admitted to our wards with Salmonella infection. Bacteriologically, a large part of the spectrum of Salmonella organisms was represented in this series. The diagnosis in each instance was based on positive agglutination reactions for both O and H antigens, the findings of a blood, urine, or stool culture positive for Salmonella, or the obtaining of the organism directly from the pus. We found positive stool cultures in about 60% of our

cases. Salmonella typhimurium predominated. It was found in one-third of our patients. Gastrointestinal symptoms were most commonly met with in our series, i. e., diarrhea, abdominal pain, abdominal distention, jaundice, and dehydration. Fever was present in every one of our patients. In two instances it was the only symptom. The spleen was enlarged in one-third of our patients. Sedimentation rates were high in those children who had complications. The white blood cell count was less than 8,000 in 30% of our patients. Marked leucocytosis, i. e., counts above 20,000, was seen in three of our patients, all of them having suffered from severe complications. Generally, the blood count showed a moderate anemia.

We encountered complications of unusual nature. One of our patients, whom we were able to follow for a period of several years, showed complete ankylosis of both hip joints. Another, who also suffered from osteomyelitis of both humeri, had to have a nephrectomy done for the relief of a pyonephrosis. A most unusual complication, never reported before, was found in one of our patients who was under observation in our hospital for a year for multiple osteomyelitis and pyoarthritis. There developed marked enlargement of the liver and spleen and an aplastic anemia which proved fatal. While appendicitis complicating Salmonella infection has been reported before, we met with an unusual experience of seeing two instances of appendicitis. One was acute catarrhal appendicitis. In this instance the diagnosis was made on stool culture after the appendix had been removed. In the other case the appendix was the site of suppuration with rupture, the pus containing a pure culture of Salmonella sp. (Type Derby). We also encountered one instance of acute peritonitis in a premature infant who was admitted for fever, abdominal distention, and swelling of the scrotal sac. It at first appeared to be a case of a strangulated hernia. On operation, pus was found to be oozing from the peritoneal cavity through the internal ring into the scrotal sac. The pus thus obtained on culture revealed Salmonella sp. (Type Derby).

There was a fatal outcome in only one of our cases. We found that therapy, whether it be with transfusion, bacteriophage, sulfathiazole, sulfadiazine, sulfaguanidine, streptomycin, or chloramphenicol (chloromycetin®), did not favorably affect the course of this disease.

DISCUSSION

DR. ROLAND C. SCOTT (by invitation), Washington, D. C.: We have recently observed three children with Salmonella choleraesuis bacteremia. These three children were treated with terramycin, and all three made uneventful recoveries. In vitro tests revealed that the organisms were extremely sensitive to terramycin as well as to aerosporin (polymixin®).

Though appraisal of the therapeutic effect of terramycin in this disease is difficult, because of the variability of duration of the untreated disease, it would appear that terramycin is more effective than the sulfonamides and the currently available antibiotics in the treatment of S. choleraesuis bacteremia.

DR. SIDNEY I. COHLAN, New York: We had an opportunity several years ago to observe an outbreak of Salmonella typhimurium infection in an obstetric newborn ward. One mother infected with Salmonella typhimurium admitted to a maternity floor created a mild epidemic which continued for several weeks. Infants in several nurseries were infected. The disease was transmitted to other mothers, and an intern and probably a nurse became carriers. Oral streptomycin therapy resulted in suppression of bacterial growth in the intestinal tract of treated infants during the time of drug therapy. Upon discontinuance of therapy all patients reverted to the carrier state. However, in view of the experience of recurring outbreaks, probably due to spread from silent carriers, it might be good prophylactic procedure to institute oral chemotherapy for all mothers and attendant personnel when a Salmonella outbreak occurs in a maternity service. The resultant bacteriostatic effect, though temporary, may be enough to prevent spread and reinfection of the nursery population.

DR. JOSEPH B. PINCUS (by invitation), Brooklyn: I merely wish to add that the children with Salmonella infection who came under our observation failed to respond favorably to the antibiotics which we employed. This was particularly true when we studied the effect of these antibiotics on rendering stool cultures negative for Salmonella organisms.

In only one case of sepsis with S. typhimurium did we think that aureomycin was effective in sterilizing the blood stream and bringing the child's temperature down to normal.

The effectiveness of this antibiotic in this case is, however, open to doubt, because the child had been ill for more than a week before admission to the hospital. In general our experience with antibiotic therapy is in agreement with that reported by Seligman and Safra, i. e., that the efficacy of antibiotic therapy in this group of infections is still questionable.

Prenatal Development of the Human Lung. Dr. Edith L. Potter and Dr. Clayton G. Loosli (by invitation), Chicago.

A histologic study was made of the development of the respiratory portion of the lung in 34 human fetuses that were distributed fairly evenly between 10 and 40 weeks. The fetuses were stillborn and were selected for their good state of preservation. Adequate fixation was assured in many by the introduction of a small amount of solution of formaldehyde U. S. P. (formalin®) or Zenker-formol® solution into the bronchial tree. Multiple blocks of tissues were embedded in paraffin and sections of each prepared with hematoxylin-eosin-azure stain for general histologic detail, azocarmine G (Mallory's "azan") stain for connective tissue, and orcein stain for elastic tissue.

The development of the lung can be divided into two principal phases corresponding to the first and last halves of pregnancy. The first phase is a period of tubular growth, the second a vascularization of this tubular structure. During the first half of pregnancy growth is by the repeated branching of tubules embedded in mesenchyme. They develop into both bronchial and respiratory portions. Blood vessels at first are separated by intervening mesenchyme from the outer surface of the tubular structures, but toward the middle of pregnancy they begin to approach the tubules and gradually come to lie closely approximated to their outer walls. When the fetus reaches a weight of from 350 to 400 gm., at about the 18th to 20th week of pregnancy, the first capillaries break through the hitherto continuous layer of cells lining the tubules and come to lie, completely devoid of an epithelial covering, in direct contact with the lumen of the pulmonary tree.

During the latter part of the first phase elastic-tissue fibers are visible in juxtaposition with the outer surfaces of the cells composing the bronchial portions of the lung. They appear in the respiratory portions of the lung simultaneously with, and in the same locations as, the first invading capillaries. Each point of capillary invasion becomes a definitive area in the final structure of the lung. Growth procedes for a time by outpouching and further branching of the cells in the zones between the ingrowing capillaries.

After they once begin, capillary invasion and elastic-tissue development progress rapidly. The capillary loops extending into the pulmonary lumens gradually become longer and develop into the septa of the alveoli. With enlargement of the capillary bed, the original cells lining the respiratory portion of the pulmonary tree become more widely separated and constantly less conspicuous.

By the end of the 28th week, when the fetus weighs about 1,000 gm., a sufficient number of capillaries are ordinarily in direct contact with the potential air space to permit adequate oxygenation of the blood in an extrauterine environment. The extent of this capillary bed increases with each passing day and is largely responsible for the decrease in mortality that accompanies increase in birth weight. At term, the original cuboidal cells lining the respiratory tubules of the early fetal lung are widely separated and inconspicuous and the alveoli are composed largely of naked capillaries that are in direct contact with the pulmonary lumens.

DISCUSSION

Dr. Clement A. Smith, Boston: I haven't the least feeling that I qualify as a morphologic expert who should discuss this paper, but I am sure that I qualify, as does everyone else in the room, as one who can say how helpful it is to see these things traced out from such a wealth of material in such a careful way.

I should like to make two points which are not at all morphologic: First, I don't think one can see the degree of lung development that is present in the fetus of 1,500 gm. or so without a feeling that the wonder is not why so many premature infants survive but why so few do. The human infant is really remarkably well equipped to exercise its extrauterine functions considerably before gestation.

Second, to see the marvelously effective system for oxygenating the blood in the lungs at term increases my respect for the human placenta, which has had that job to do before the time of birth. This reenforces certain feelings I have about the remarks that Dr. Clifford will make later about what happens when the infant may be forced to rely upon a placenta which begins to lose effectiveness through relative senility.

DR. HERBERT C. MILLER, Kansas City, Kan.: Dr. Potter is to be complimented on this beautiful presentation. My question is an oblique one, but I think it is pertinent because the title of her paper is "Development of the Lung." Two or three years ago Dr. McMahon came out with a concept of the alveolar dysplasia, a congenital disorder, and Dr. Potter subsequently took issue with him. Very recently in the *A. M. A. Archives of Pathology*, a group from Western Reserve University have come out with an investigation which completely supports Dr. McMahon's thesis. In view of the fact that Dr. Potter has studied many hundreds of lungs of newborn babies and fetuses, I wonder if she would be willing again to comment on whether congenital alveolar dysplasia exists or does not exist.

DR. JAMES B. AREY (by invitation), Philadelphia: Dr. Potter has demonstrated very beautifully the wide separation of the pulmonary alveolar spaces from the alveolar capillaries in the premature infant. Some authors have suggested that the hyaline membranes in the lungs of newborn infants may be related to the resorption of fluid which is normally present in the alveolar spaces. It would seem probable that less fluid would be absorbed from the alveolar spaces of the premature infant than from those of the full-term infant, as the interalveolar capillaries of the premature are farther removed from the air spaces than are those of the full-term infant. Nevertheless, hyaline membranes occur much more frequently in the premature infant than in the full-term infant. Would Dr. Potter care to comment on this theory of the origin of hyaline membranes and on its relation to the anatomical findings which she has demonstrated?

DR. HARRY H. GORDON, Denver: I think it is worth pointing out that just as part of the maturation of respiratory function depends upon a development of capillaries and a disappearance of cuboidal epithelium, so part of the maturation of renal function also depends on a development of capillaries and a disappearance of cuboidal epithelium.

DR. EDITH L. POTTER, Chicago: It is always a little dangerous to say a thing someone else describes does not exist. I have never had an opportunity to examine the slides of the cases that have been described as alveolar dysplasia, but from the published pictures it appears that the condition described is actually caused by a hyaline membrane and secondary resorption of air. We have had an opportunity now to do autopsy examinations on about 8,000 fetuses and newborn infants. I have looked at the sections of the lungs of all of those babies myself. I have never seen congenital alveolar dysplasia, and the authors who are writing on this subject would lead you to believe that it occurs in a very high percentage of cases and that it is unrelated to any other disturbance, that it is an actual cause of death.

This is not the appearance that would be produced by a malformation of the lung that would inhibit the development of alveoli. All that is necessary to disprove the contention that such lungs are malformed is to inject fluid into the trachea and watch these alveoli open up. One is quickly convinced that what on ordinary preparations looks like a solid, undeveloped mass is actually nothing except a generalized absence of air and that the great engorgement of the capillaries contributes to this appearance.

The lungs that we have seen with a similar pattern we have been unable to expand by air, but when fluid is introduced, it works its way into the interstices between the collapsed structures, and they open up and appear as perfectly normal lungs as far as the developmental histologic pattern is concerned.

The hyaline membrane is a thing about which we have already heard and about which we are going to hear a good deal more. It is an extremely important cause of death. In our hospital between 1939 and 1949 it accounted for 40% of the premature deaths and for all the deaths of the babies after delivery by Caesarean section who were not malformed or who did not have erythroblastosis.

One other comment in answer to Dr. Gordon, I meant to imply that there is no shedding of the cuboidal cells that line the tubular structures of the premature lung. In fact, one of our primary theses is that there is an ingrowth of capillaries with a separation of cuboidal cells and that at no time can you see a shedding of the cells that originally lined these spaces. We believe that such cuboidal cells are probably present in just as large numbers at the time of birth as they were in the early stages and that it is simply a matter of further growth and capillary penetration that makes it seem that they are present in much smaller numbers.

Cor Pulmonale in Infancy and Early Childhood. Dr. Stephen Royce (by invitation), San Marino, Calif.

Pulmonary heart disease is not rare in childhood and may even complicate the neonatal period. The differential diagnosis from congenital cardiac disease is often difficult, especially in the first months of life. When extensive respiratory disease precedes or accompanies congestive failure, the newborn is seldom considered to have secondary cardiac damage, even though he may lack good evidence of primary heart disease. In older children with profound lung damage—especially that associated with fibrocystic disease of the pancreas—death may be preceded by congestive failure, and postmortem examination often reveals evidence of chronic strain of the right ventricle. Recently it has been realized that this sequence of pulmonary disease, pulmonary hypertension, right ventricle strains, and subsequent myocardial hypertrophy can occur in earliest infancy. And it may occur in a relatively short period, often less than four weeks.

Clinical and autopsy data are presented on 34 patients, the youngest aged 10 days and all except two under 6 yr. In 28 patients there was underlying fibrocystic disease, with its characteristic lung changes. An explanation is offered for the rising incidence of pulmonocardiac failure in this condition and for its high incidence as compared with that of other severely destructive lung diseases of childhood. Bronchiectasis and tuberculosis, for example, rarely produce cor pulmonale, and the asthmatics escape entirely.

Anatomical verification of the diagnosis is essential. During life there is a confusing overlap of respiratory and cardiac signs, and laboratory work may be directly misleading, e. g., in roentgen examination the heart shows a relative decrease in size as the lung disease progresses. Cardiac catheterization now makes antemortem diagnosis feasible. Studies of the pulmonary pressure in children with fibrocystic disease and in children with chronic asthma are presented.

The diagnosis of cor pulmonale assumes greatest interest at the infant level. It is now clear that otherwise mysterious episodes of infant cardiac failure have been on the basis of pulmonary disease. Approximately one-half the patients with cor pulmonale have terminal decompensation and die with severe right-sided cardiac failure. This may occur suddenly, only a few days after the first signs of chest disease, or may come on gradually after many years. The duration of disease bears an inverse ratio to the severity of the initial insult. Massive overloading of the pulmonary circulation by blood-borne foreign bodies may cause immediate death, and fibrocystic lung disease may produce such abrupt pulmonary hypertension that the patient survives only a few days. But most infants and children are able to compensate after the initial strain and show a gradual progression to the decompensated state over a period measured in years. The relation of cardiac findings at autopsy to duration of respiratory disease is outlined.

Dr. Helen Taussig, Baltimore: I have not much to contribute but I wish to congratulate Dr. Royce on the paper and his presentation. We have seen cor pulmonale in infants and young children, I believe five or six cases, without any pancreatic disease or cystic disease. As we look for it, I think we will find it is commoner than we have suspected, but our group of cases actually is quite separate from the group here reported. I am sure that the condition is real and that it does exist.

Dr. Forrest H. Adams (by invitation), Minneapolis: I am wondering if the author would object to using the term "pulmonary hypertension" instead of "cor pulmonale." It seems to me it

gives us a little better understanding of what is taking place physiologically. I should like to agree with what Dr. Taussig has just said, namely, that there are apparently patients with primary pulmonary hypertension in the pediatric age group.

Dr. Jesse Edwards at Mayo Clinic is particularly interested in pulmonary hypertension from a pathological point of view, and he has a concept regarding the changes in the muscular pulmonary arteries in these cases. I wonder if the author of this paper has any particular observation with regard to the pulmonary arteries in these patients he has studied pathologically.

DR. HENRY D. LAUSON (by invitation), New York: I should like to add my sincere compliments to the author for this very clear description of a process that only recently has been receiving the attention that it deserves in adult cardiology.

I should like to ask one question: in the child who is beyond infancy might it be a good idea to restrict activity, since that seems to be a very worthwhile procedure in the adult?

DR. STEPHEN W. ROYCE (by invitation), San Marino, Calif.: Thank you very much for your comments. In answer to Dr. Taussig, we, too, have seen scattered cases of what we call cor pulmonale in other types of chest disease. Fibrocystic disease, of course, does constitute the bulk of our cases. We have seen it occur in bronchiectasis and diaphragmatic hernia, but those cases are extremely rare. We have not seen it in chronic asthma.

Dr. Adams, I do not object to using the term "pulmonary hypertension" instead of "cor pulmonale." I think that when we talk about cor pulmonale in association with fibrocystic disease, we are using a very poor experimental animal. A child with fibrocystic disease certainly has pulmonary hypertension; he has extreme degrees of anoxia; he has lost most of his elastic tissue (the development of which Dr. Potter outlined in her paper), and he has also a loss of capillary tissue. At the present time we are studying both in vivo and at postmortem examination the effects of hypertension and hope to have some answers on that next year.

In answer to Dr. Lawson's question about the restriction of activity in the older child, our experience is limited to the younger age group. Restriction is indicated but probably not necessary, since the child is acutely aware of his oxygen deficit. Studies in adult emphysema show that anything which causes the slightest degree of hyperventilation is deleterious to the patient.

It is interesting that the onset of cardiac disability often appears to coincide with a sudden decrease in the exercise tolerance. Until late in their course many of the fibrocystic patients show a surprising amount of activity. They tend to be rather wiry and muscular, and, although chronically dyspneic and conservative of excess motion, they play with moving toys and take an argumentative interest in other patients and in the proceedings of the ward. Then there often occurs a sudden change; the child becomes extremely quiet and disinclined to make the slightest movement. The children progress from here into a continuously uncomfortable state, querulous and unhappy about anything that requires the slightest effort. This may represent the earliest clinical evidence of pulmonary heart disease.

Direct Relief of the Pulmonary Stenosis in Tetralogy of Fallot (Brock Procedure).

DR. D. F. DOWNING (by invitation), DR. CARL FISCHER (by invitation), DR. C. P. BAILEY (by invitation), DR. R. P. GLOVER (by invitation), and DR. T. J. O'NEILL JR. (by invitation), Philadelphia.

During the past six years probably 3,000 or 4,000 persons with cyanotic heart disease have been subjected to surgical operations. Most of these procedures have been for the relief of the pulmonary stenosis found in the complex cardiovascular defect known as tetralogy of Fallot or at least a closely related malformation. In its classical form tetralogy of Fallot embraces (1) pulmonic stenosis, which may be present as a stricture or hypoplasia of the main pulmonary artery, stenosis of the pulmonary valve, or stenosis of the infundibulum of the right ventricle, whether this be a general narrowing of the outflow tract or a true infundibular septum; (2) high intraventricular septal defect; (3) overriding of the aorta—straddling of the interventricular septum so that the aorta acts as the outlet of both ventricles, and (4) hypertrophy of the right ventricle undoubtedly secondary to the high intraventricular pressure produced by the pulmonary stenosis and the consequent necessity for the right ventricle to compete constantly with the left in ejecting its contents.

The vast majority of the operative procedures so employed have consisted in the definitive creation of an artificial patent ductus arteriosus by either the Blalock or the Potts method. The artificial ductus reroutes a portion of the mixed venous and arterial blood in the aorta back to the pulmonary artery and lungs for more complete oxygenation. Such shunts have proved amazingly effective in relieving the cyanosis and improving the patient's ability to undertake physical exertion. However, even in the most satisfactory cases in which this management is used, there is usually perceptible enlargement of the heart shadow, and there is always persistent undersaturation of the systemic arterial blood. The levels of saturation after successful operation usually are from 70 to 80%, rarely being as high as 85%. It is generally believed by thoracic surgeons experienced in this work that congestive heart failure ensues within two years of operation in about 10% of cases. The artificial patent ductus arteriosus certainly threatens or forbodes the possible development of the usual complications of untreated natural patent ductus—limited myocardial reserve, congestive heart failure, and subacute bacterial infection. However, so Blalock has said: "We can not let these patients die of asphyxia today because of fear of possible heart failure in the distant future."

Russell Brock, dissatisfied with the inefficiency, from an engineering standpoint, of the cardiovascular system after a successful shunt procedure, restudied the pathologic changes found in these patients at autopsy. He became convinced that a direct attack upon the pulmonary stenosis was feasible in most cases and that this defect was the primary one of the malformation complex. He has shown that once the pulmonary stenosis is overcome, the other defects may be tolerated with ease. Brock has also successfully applied this method in cases of so-called isolated or pure pulmonic stenosis, and it has met with general acceptance by the profession for that lesion which is unresponsive to any shunt operation.

Our work, which merely confirms and extends Brock's ideas, so far embraces 25 consecutive cases of tetralogy and four of "pure" pulmonic stenosis in which treatment was by the direct method. The mortality has been 20% in tetralogy, most of it among several very young infants so treated. Our surviving patients are most satisfactory, with complete relief of cyanosis, practically normal physical capacity, and an arterial oxygen saturation routinely in excess of 90%.

We feel that the inherent mortality of this procedure is no greater than in the shunt procedure. We feel that it is much better to reduce the number of cardiovascular defects by eliminating the primary and major one than it is to add a fifth cardiovascular defect (patent ductus arteriosus) even though partially compensatory, which by its very anatomical existence usually requires surgical correction.

We believe that once the pulmonary stenosis is overcome, the entire right ventricular ejection will follow the line of least resistance up the low pressure pulmonary artery, rather than across the septal defect into the left ventricle or up the higher pressure aorta. Thus the circulation becomes functionally essentially normal.

Dr. Helen Taussig, Baltimore: I have listened with great interest to this paper, and naturally I rise in defense of our own team. In the first place, we have not found valvular stenosis in the tetralogy of Fallot nearly so common as they have in Philadelphia. We all agree that valvular stenosis with no ventricular septal defect should have a Brock operation. We further agree that if you had a ventricular septal defect with no demonstrable overriding of the septum and valvular pulmonary stenosis, a Brock operation should be done.

When it comes to dissecting out part of the interior of the ventricle, in many instances the stenosis is so extreme that it would be very difficult to dissect through it. If you only dilate a little, the question is how long will the benefit last? In one instance in which Dr. Blalock has tried it, the child was improved for a short time, and then the stenosis apparently returned, and the child died in right-sided failure. At autopsy we could see no indication of any dilatation. That patient had a tetralogy with infundibular type of stenosis.

The real question is whether you can take out a bite of tissue and not subsequently have contraction of the scar. Dr. Blalock has done a few direct approaches with success, and on the whole he has been pretty discouraged; he has had nearly as high a mortality rate as has been reported here. On the other hand, we have had extremely good results from anastomosis. Those of you who were present at the meeting of the Association of American Physicians heard

my report on our first 1,000 cases, and the over-all mortality rate on all types of pulmonary stenosis and atresia has been 14.4% in the immediate postoperative period, with a 15.5% over-all mortality six months after operation.

My feeling today is that if in a patient with a tetralogy severe cardiac failure develops after anastomosis—immediately, six months, two years, or even six years—it is probably an error in diagnosis. If the patient survives operation and is doing well six months after operation, I honestly expect him to do well; indeed, if progressive cardiac enlargement develops, I think I have missed my diagnosis.

A few patients have failed to do well in that polycythemia has again developed; this is particularly true of the little children. I do not feel that the anastomosis grows as well as a normal vessel. Seventeen patients have required a second operation.

Whether, over a period, the direct approach is going to show better results, or whether there is going to be scarring down and development of trouble later on, is going to take a long time to tell.

The question of subacute bacterial endocarditis is also going to remain unanswered. You do not have a normal heart in either case. You have some scarring at the site where you have bitten out the infundibular stenosis and some irregularity where you have cut the valve. They are not normal valves. As regards subacute bacterial endocarditis, we admit that in the early postoperative period any raw surface is susceptible to subacute bacterial endocarditis. Of the group of 844 in the early postoperative period, we have had 11 patients with subacute bacterial endocarditis. For the other group, for which it has been three months to six years, since operation, the incidence is still under 1%, six of 800 patients. We have had only two deaths from subacute bacterial endocarditis in that group; consequentlly, this is not a very serious objection to the operation.

I should like to ask whether, in the direct attack on the fundibulum, you have had any aneurysms of the right ventricle. In going through the right ventricle before the smaller Potts instrument became available, in a couple of instances we were much worried about a bulge in the right ventricle. If you go through the right ventricle and cut out too much, I would still be worried that this would form a weak point in the myocardium.

With regard to the constriction of the pulmonary artery, I think I have seen one at operation that looked as if the constriction occurred about 1 cm. beyond the valve. The question is how long dilatation alone is going to hold. With a tetralogy, a bypass operation would hold.

While we are still able to say that a child has an 85 to 90% chance of coming through the operation and at least an 80% chance of maintaining that improvement, we are still standing by the Blalock operation.

Dr. R. P. Glover (by invitation), Philadelphia: I wonder if anybody would like to have my job right now of trying to clear up anything after Dr. Taussig, with her experience, has spoken. I certainly cannot answer many of the questions, and I think she was very kind to us in not giving us a little bit more of a broadside, which we thought we might get.

We realize, of course, that we are treading on very precarious ground. We have had, at present, 30 consecutive cases. Dr. Taussig has presented 1,000. Dr. Potts and Dr. Gibson have 500, and many others have many more. We do not intend this paper to be anything approximating a final decision on the subject at all. We present it as a preliminary report. We present it from this standpoint: We saw 30 consecutive cases of tetralogy of Fallot; we did this operation; we found what we found at operation, and our results are these, which have already been given to you, so that I do not think we need to go any further into it than that.

With regard to valvular versus infundibular obstruction, this was not a pathological paper. We merely reported what we found, and we find it hard to believe ourselves—very hard. Nevertheless, 15 of the patients were treated as though they had valvular obstruction, with good result. Some of those may have been immediately subvalvular; we do not know. The patients fortunately, are living, and we have not determined that. The two of the 15 that died had valvular obstruction.

We, defending our position, do not feel that the removed area, or what is left behind after we remove part of the infundibulum, will scar any more than Dr. Blalock or Dr. Potts feel that their anastomosis will close. The direct attack may well produce an area of weakening. In

two cases we have noticed a bulge that occurred in the area where we have opened into the ventricle; so that we are just as concerned about what is going to happen to those areas as is Dr. Taussig. We do not know what is going to happen. Nothing has happened yet.

With regard to the raw surface and the possibility of subacute bacterial endocarditis, in none of these cases has it developed. We have operated on something like 200 patients with mitral stenosis and opened them and left behind a raw surface, and in none of them has subacute bacterial endocarditis developed; that is as far as we can go on that score.

We realize our mortality is a little high, an operative mortality of 20%. Let me remind you that when the first 144 cases of tetralogy of Fallot in which treatment was by the shunt procedures were presented, the mortality was 22%. We are just in the beginning stages of use of this procedure, and possibly our mortality will improve as the others do. We feel at the present time that it is incumbent upon somebody to investigate the possibility of providing the cyanotic child with a more efficient circulation than that with its inborn defects to which an arterial-venous fistula has been added. We are almost as willing to prove ourselves wrong—"almost," I say—as right. We would like to know the answer, and at least the possibilities should be investigated.

Postmaturity. Dr. Stewart H. Clifford, Dr. Duncan E. Reid (by invitation), and Dr. Jane Worcester (by invitation), Boston.

The 10-yr. obstetric life histories of a consecutive series of women admitted to the Boston Lying-in Hospital since January, 1940, have been analyzed, the study continuing until a total of 5,000 deliveries had been accumulated.

The data from 2,187 women of gestational age 200 days and over, who had had one and only one delivery in this hospital during the 10-yr. period 1940 to 1950, are given in the tabulation:

Gestational Age Group, Days	No. of Pregnancies	Incidence, %	Neonatal Mortality, %	Fetal Mortality, %	Total Pregnancy Wastage per 1,000
200-259	199	9	5.1	11.6	161
260-269	223	10	0.9	2.7	36
270-289	1,324	60	0.5	1.2	17
290-299	318	15	1.0	2.8	38
300-339	123	6	1.8	10.0	114
Total	2,187	100	1.1	3.0	41

In this group postmaturity ranks close to prematurity in defining a group experiencing high neonatal and fetal mortality. The premature group, 9% of the deliveries, accounted for 36% of total pregnancy wastage. The postmature group, 6% of deliveries, contributed 16% of total wastage. The two together, with 15% of deliveries, were responsible for 53% of pregnancy wastage.

The vital statistics of the group with a gestational age of 300 to 339 days in which the mothers had two or more pregnancies in the 10-yr. study period are compared with those for the "one-delivery" group in the following tabulation.

Gestational Age Group, 300-339 Days	No. of Pregnancies	Neonatal Mortality, %	Fetal Mortality, %	Total Pregnancy Wastage per 1,000
One delivery	123	1.8	10	114
Two or more deliveries	103	1.1	1	20
Total	226	1.4	5.8	71

Ninety per cent of the mortality encountered in the postmature group was contributed by the women that have had one and only one delivery in the hospital since 1940. Three-fourths of all deaths due to postmaturity were children of primigravidae who had had one and only one delivery since 1940.

The average age of the primigravidae with dead babies was 29 yr. One-half of the fetal deaths occurred before the onset of labor; the duration of labor in the remaining primigravidae was 34 hr. The average length of labor in primigravidae whose infants survived was 17 hr. in both those with "one-delivery" and those with "two or more deliveries." The average length of labor in secundigravidae and over whose infants survived was 10 hr. in all gestational age groups.

Postmaturity presents a peculiar hazard to the primigravida; after 300 days' gestation one in every 10th infant died. For the primigravida 26 yr. of age and over who delivers after 300 days, one in every three babies died. Prolonged labor and increased maternal age are but partial explanations. In gestational age groups beyond 300 days half of the fetal deaths occurred before the onset of labor. The barren years that follow in 73% of the patients having a gestation of 300 days or more demands explanation. The increased incidence of congenital malformations in postmature infants of primigravidae is also unexplained.

From this preliminary investigation, postmaturity, defined above on the basis of gestational age, is found to rank with prematurity as a cause of pregnancy wastage.

DISCUSSION

DR. MYRON E. WEGMAN, New Orleans: Dr. Clifford's analysis at the Boston Lying-in Hospital is in close accord with several studies which Dr. Baumgartner and a few of us did in the New York City Health Department some years ago (*Pediatrics* **6**:329 [Sept.] 1950). We studied the certificates from more than 200,000 live births and the associated fetal and neonatal deaths, using a technique which might be helpful in studying the Boston material. Miss Marjorie Bellows suggested to us that our data were susceptible of analysis by a life-table method, in which one considers as the base line the number of infants who are still unborn *in utero* at each time period during gestation. The life-table method permits delineation of the progressive change in fetal death rates in relation to the number at risk, that is, the number of fetuses still *in utero* at the time the fetal death took place, rather than the number who happened to be born at that time. Unfortunately, we had no accurate data by days, as Dr. Clifford did, but used increase in weight as an approximation of the change in time.

The fetal death rates for boys, so calculated, started at 9.9 per 1,000 at a weight under 1,000 gm., dropped to 3.2 per 1,000 at 1,500 to 1,999 gm., rose slowly to 9.7 per 1,000 at 3,500 to 3,999 gm., and then rose steeply to 184.5 per 1,000 at 5,000 gm. and over. These data support the thesis that the overweight children are subject to high mortality rates.

Two other points are of importance: First, in any analysis of this sort it is extremely important to take into consideration both sex and race. We found that the mortality rate for girls was consistently under that for boys in the lower-weight groups but consistently higher than that for boys in the upper-weight groups. It is a great rarity to find an instance in which boys have a lower mortality than girls. Distinctions in relation to race are only partially similar, perhaps owing to differences in quality of care received, but nonwhite infants have higher rates than white infants in each of the higher weight groups.

Secondly, we made an analysis in our series of what might be called the "best birth weight." If one combines the material on fetal death rates with that on the neonatal deaths, one can arrive at a point where the infant will have the best chance if he is out of the uterus; that is, if he has left the uterus earlier or stays in the uterus longer, his chances of dying, as either a fetus or a neonate, become greater. I do not want to be misunderstood on this. This does not mean necessarily that he ought to be taken from the uterus at that point, but on the basis of direct observation he has the best chance if he does come out then. Our observation was based on figures for a large and cosmopolitan city and should not be taken as necessarily having significance elsewhere. For interest it may be noted that our "best weights" were 3,000 gm. for boys, 2,880 gm. for girls, 2,990 gm. for white infants, and 2,830 gm. for nonwhite infants.

DR. AMOS CHRISTIE, Nashville: I should like to congratulate Dr. Clifford on this analysis. Everyone knows his contribution to the field of prematurity, and now he is attempting to reduce the neonatal mortality due to postmaturity.

I should like to ask him whether he has tried any technique of predicting postmaturity, such as fetal bone density, ossification-center visualization, or fetal encephalometry, to which he contributed so much in the early phases of study of the premature problem. I ask this question because my colleagues and I have also been interested in this problem and have been trying to make some contribution to our obstetric colleagues and the offspring that we are responsible for in the pediatric service at Vanderbilt University Hospital. Our study has been by means of visualization of the fetal parts, specifically the ossification centers. All of us know that there is a larger number of any one ossification center as both weight and length increase, and we know the wide individual variations which Dr. Washburn and others have taught us. We also know the sex and the race differences and variations which Dr. Wegman referred to. Nevertheless, it was possible, with the aid of our colleagues in radiology, to develop excellent visualization of fetal parts, and then it was quite obvious that the presence of a center, or centers, or combinations of centers, or, shall we say, their absence, indicates with some certainty that immaturity or prematurity exists.

With this technique, it is possible to predict with considerable accuracy the presence of prematurity or low birth weight, and consequently physiologic immaturity. The same technique might be used to study postmaturity.

DR. EDITH POTTER, Chicago: I should like to ask Dr. Clifford what his data show in relation to the anatomic development of the fetus and the infant, whether there is the same type of correlation with increasing fetal size that there seems to be with fetal age.

Obstetricians have recently reawakened their interest in postmaturity. We go through cycles, as far as attempting to deliver the infant at the optimum time is concerned, and 10 or 15 years ago we were delivering a great many patients by induction if they did not go into labor at the expected time. The abnormal type of labor that results from an induction in case the patient is not ready to go into labor leads to an increase in infant mortality. I think we must be careful in our interpretation of data on mortality in relation to gestational age so that we do not let our enthusiasm for delivering the baby at the optimum time run away with our good judgment.

There is one interesting piece of work which bears on this problem that Dr. Clifford, I am sure, would have mentioned if he had had time. Many years ago Dr. Franklin Snyder and others showed that if they gave injections of corpus luteum hormone to the rabbit and lengthened the pregnancy from 31 days, which is the normal time, to 36 days, they had 100% fetal mortality due, presumably, to failure of the placenta.

DR. JAMES B. AREY (by invitation), Philadelphia: In view of the postmaturity, the splanchnomegaly, and the congenital malformations noted in this group of infants, would Dr. Clifford care to comment concerning the incidence of diabetes mellitus in their mothers? It is recognized that prediabetic mothers may give birth to infants with all the pathologic changes of the infants of diabetic mothers. Have any of the mothers of these infants acquired diabetes mellitus subsequent to delivery?

DR. STEWART H. CLIFFORD, Boston: The work of Drs. Wegman and Baumgartner has an important bearing on the present study. This work and a conference sponsored by the Children's Bureau, in which the role of postmaturity in pregnancy wastage was considered, were the major reasons the present investigation was undertaken.

The material available to us is practically all from the white race. As yet, we have not analyzed our data to determine the influence of sex.

Dr. Potter's warning is important and timely. Dr. Wegman's data on "optimum weights" for birth, Dr. Christie's ability to define postmaturity by roentgenography, and our data showing high mortality for babies of more than 300 days' gestation must not be taken as a recommendation to induce labor when a baby becomes postmature. The group is too large, one in every 20 pregnancies, and much more harm to both mother and baby would result from induction of labor than if nature took its course. There is a very small group of mothers over 26 yr. of age in their first pregnancy who will lose every third baby when pregnancy exceeds 300 days. This will be an important group in which to reappraise obstetric management.

In answer to Dr. Arey's question, none of the mothers of the postmature babies in this series were diabetic, and we have no record of any subsequently developing diabetes. The babies from mothers with severe diabetes are frequently seen with a clinical picture resembling that of postmaturity—there is apparently a growth stimulus that makes these babies physiologically postmature for their given gestational age.

In response to Dr. Potter, we found similar results using each of the three criteria generally available for measuring maturity. In picking out a group of postmature infants of high mortality, the criterion of birth length appears to be the best, that of gestational age next, and that of birth weight the least effective.

Development of Chemical Homeostasis in Newborn Infants. Dr. Bruce D. Graham (by invitation) and Dr. James L. Wilson, Ann Arbor, Mich.

This paper is concerned with the demonstration of the development of electrolyte homeostasis in the normal newborn infant as compared with standards established for premature infants and for adults. Data were collected to compare capillary blood levels for the following factors during the first days of life of normal newborn infants: blood pH, plasma carbon dioxide, chloride, and total base, total serum proteins, and, by subtraction, the "R" component in the Gamble diagram. Results are compared with data secured in this laboratory previously on a group (73) of premature infants and an adult control series, using the same laboratory methods. A concomitant study of the relationship of maternal anesthesia and analgesia to blood oxygen saturation, blood carbon dioxide tension, oxygen content, and blood pH of the newborn infant is also presented.

Sixty-six newborn infants were studied, all products of normal deliveries. No attempt was made to include abnormal deliveries in this study. All infants remained relatively well during the neonatal period and were, so far as could be determined clinically, developing into physiologically normal infants. The mothers' ages ranged from 19 to 38 yr. and previous pregnancies from none to nine.

Capillary blood samples were drawn under oil for the determinations listed. The R-fraction of the acid-base balance was determined by subtraction of the above-named components from the total base value. Blood oxygen saturation was calculated from values obtained for oxygen content and capacity. The carbon dioxide tension was calculated by the Henderson-Hasselbalch equation from values obtained for blood pH and carbon dioxide content. Samples were taken from all infants within the first hour of life. Of every four infants, samples were taken again from one at 4, from one at 8, from one at 12, and from one at 24 hr.

Of these 66 infants studied, 30 were delivered from mothers who received caudal analgesia, 15 from mothers who received saddle block analgesia, 9 from mothers who received nitrous oxide anesthesia, and 12 from mothers who had drop-ether anesthesia.

Results of the study revealed that most full-term infants at birth are in a state of metabolic acidosis, with a lowered blood pH and plasma carbon dioxide content, but have essentially normal plasma chloride and total base values. The majority of these infants within a few hours have a blood pH of adult level but maintain for some time a lowered carbon dioxide content. The calculated carbon dioxide tension reveals that, although the infants have a carbon dioxide tension at birth within the adult normal range, it drops and remains below the adult range throughout the remainder of the first day.

Comparison of blood oxygen content, carbon dioxide content, percentage of oxygen saturation, and blood pH, with relation to the maternal analgesic and anesthetic agents mentioned above, revealed no apparent significant effect of these agents on the infant either at birth or subsequently during the first day of life.

DISCUSSION

Dr. Harry H. Gordon, Denver: In Dr. Graham's slides, we saw comparisons between full-term babies at birth and premature infants at all ages. I should like to ask what the data show when a comparison is made with premature infants just after birth. This is of some interest because it has been suggested that the high total base and the high chloride levels in premature infants may be associated with the amount of electrolytes in their feeding.

DR. CLEMENT A. SMITH, Boston: I think I can guess the answer to Dr. Gordon's question. These data probably will indicate that the full-term newborn infant is a much more standardized organism than the premature infant at almost any age. I do not know how much more standardized he is than the premature infant on the day he would have been born, but I dare say that Dr. Graham, if his results are at all like ours, will have found that the premature infant does not seem to regulate his body chemistry and physiology very strictly in these essential matters as the days after his birth go by.

The entire subject is one that interests me greatly, and I am glad to see these data being collected. They seem to show the interesting fact that the younger the organism is, the wider the range of physiologic latitude nature fortunately seems to have designed him to tolerate. Although, on the one hand, he is unable to bring himself into line if he is a very young and premature organism, on the other hand, he seems to be less disturbed by this instability than if he were a mature organism.

DR. JAMES N. ETTELDORF, Memphis: We have just completed a study of the plasma and erythrocyte chemistry (*Pediatrics* **7**:565 [April] 1951). This study was conducted on approximately 200 infants from full-term to 2 yr. of age. We made some observations which coincide with the report just given. We found, for instance, that the pH and chloride values coincide; the bicarbonate level in our experience was slightly higher than that reported by Dr. Graham. We found a close parallelism between the plasma sodium of the mother and that of the infant at birth, with a low value of 134 mEq. per liter prevailing. The plasma sodium did rise to a normal level after 24 hr. and remained constant thereafter.

The plasma potassium in the maternal venous blood was low but usually within normal range. The infant's plasma potassium was slightly elevated at birth, and in the umbilical arterial blood it was elevated considerably. Such elevation is to be expected when one considers the anoxia and cellular destruction in the placenta at the time of birth.

In our erythrocyte studies we made one interesting observation. The erythrocyte sodium tended to become elevated a few days after birth and remained 25% elevated above the normal figure of 15 mEq. per liter for adults; we obtained a figure of approximately 20 mEq. per liter, and the value remained high until 17 mo. of age.

The plasma calcium concentration between the first month and the second year stayed at a remarkably constant level of 5.3 or 5.4 mEq. per liter until 15 mo. of age. A slight reduction to 5.1 mEq. per liter was obtained after 19 mo. of age.

The plasma protein concentration, blood nonprotein nitrogen, and hematocrit were also studied but will not be commented upon at this time.

DR. BRUCE D. GRAHAM, Ann Arbor, Mich.: I cannot answer Dr. Gordon's question directly, except to say that when this study was made we had only one premature infant in the first day of life. However, we did break the data on these infants down into age groups and could find no statistical difference in values obtained on any of these determinations when grouped by the ages of the infants in weeks.

The study done by the Memphis group helps complete the picture. The discrepancy in the carbon dioxide content is the difference between venous blood (their study) and capillary blood (our study). A study from our laboratory, unpublished, on a group of persons from whom we obtained arterial capillary, and venous samples revealed the carbon dioxide level in venous blood to be 2 or 3 mEq. per liter higher than that found in capillary and arterial blood. We did not fractionate the total base for potassium and sodium.

Some Clinical and Metabolic Responses of Premature Infants to Corticotrophin (ACTH). DR. SAMUEL Z. LEVINE, DR. HENRY L. BARNETT, DR. C. WARREN BIERMAN (by invitation), and HELEN MCNAMARA (by invitation), New York.

Most premature infants receiving vitamin C-free diets of cow's milk excrete intermediates of tyrosine in their urine. These intermediates are *p*-hydroxyphenylpyruvic acid and *p*-hydroxyphenyllactic acid. This metabolic defect is corrected by ascorbic-acid administration. Heretofore, no other agent has been consistently effective. The close interrelations between vitamin C and adrenocortical function prompted a study of the effect of corticotrophin (ACTH) and some adrenocortical steroids on this tyrosyluria, on body weight, and on clinical behavior.

It was found that the metabolic aberration was corrected in all 18 observations on 17 premature infants who received 12.5 mg. or more of corticotrophin daily for three and one-half or more days in a total dosage exceeding 60 mg. The administration of five adrenocortical-like steroids (desoxycorticosterone acetate, testosterone, progesterone, and compounds A and L), and epinephrine, in the dosages given, was wholly ineffective. Treatment with cortisone in total dosages of 350 mg. or higher corrected the defect inconstantly (in three of eight observations).

The administration of corticotrophin was associated with a sequence of body-weight changes which was identical in all infants as follows: (1) substantial weight gains in the foreperiods; (2) marked decline in the rate of weight gain, or even weight loss, in the test periods; (3) accelerated weight gains in the afterperiods; (4) average weight gains for the combined test-periods and afterperiods which closely approximated foreperiod levels.

The alterations in body weight during corticotrophin therapy were accompanied with striking changes in clinical behavior: hyperactivity, vigorous crying, and ravenous appetities. Systemic pallor, often associated with local blanching at the site of injections was a frequent accompaniment. These clinical responses returned gradually to pretreatment patterns with cessation of therapy. The effect of the adrenocortical steroids on these features was by contrast negligible.

Metabolic balances of two infants, who received 250 and 350 mg. of corticotrophin for five and seven days, respectively, showed that balances for nitrogen and sodium became negative during treatment. Potassium balances decreased less strikingly, and changes in phosphorus balances were irregular.

A significant degree of glycosuria appeared in 20 of 22 infants receiving corticotrophin, but it was not observed with the adrenocortical steroids, including cortisone, in the dosages given. The number of circulating eosinophils was consistently depressed by continued corticotrophin administration, but the response four hours after the initial dose was less than that observed in older subjects. Eosinopenia after administration of cortisone and the other steroids was insignificant.

DISCUSSION

Dr. Harry H. Gordon, Denver: These uniform results with corticotrophin therapy are indeed exciting, when one considers the inconstant results we have obtained with various hemopoietic agents. I would like to stress one point that has been made by Dr. Levine. It is a point well stated by Sayers, namely, that in our thinking about the various hormones we should be more concerned with the target cells.

Dr. Robert Klein (by invitation), Pittsburgh: I think one point Dr. Levine brought out should be re-emphasized. Newborn infants, both full-term and premature, lose sodium when given corticotrophin, and I think the weight loss can be accounted for successfully by correlating it with the increased urinary volume that accompanies this sodium loss.

Dr. Samuel Z. Levine, New York: The work reported by Dr. Silverman and Dr. Day from Babies Hospital, New York, paralleled the results we obtained with respect to weight gain and clinical behavior. I think Dr. Gordon's comment with respect to the target cell and the comment with respect to the differences in reaction can be discussed together.

The study mentioned dealt with full-term newborn infants and adults; we observed premature infants ranging in age from 11 to 58 days. It is conceivable that the reaction to corticotrophin in the premature at that particular period might be different from that in other persons because of differences in response of the target cells.

Observations on the Availability of Vitamin E in the Newborn. Dr. P. György, Dr. G. M. Cogan (by invitation), and Dr. C. S. Rose (by invitation), Philadelphia.

The red blood cells of rats kept on a tocopherol-free diet may be hemolyzed in vivo and in vitro by small amounts of dialuric acid, a reduction product of alloxan, or by hydrogen peroxide. Tocopherol in small amounts protects both in vivo and in vitro such red blood cells from the hemolyzing effect of dialuric acid or hydrogen peroxide. The newborn litter of rats fed a normal stock diet (mixed grains and greens) shows a positive hemolysis reaction, whereas, simultaneously, the red blood cells of the mother animal exhibit no hemolysis under the influence of

dialuric acid or hydrogen peroxide. Thus, it may be assumed that the mother animal is sufficiently supplied with vitamin E and the newborn litter is deficient in vitamin E. Six to 12 hr. after birth, the hemolysis reaction becomes negative in the newborn animals, probably under the influence of the colostrum, which is rich in vitamin E.

The red blood cells of newborn infants show mild but distinct hemolysis when exposed to dilute solution of hydrogen peroxide, but not to that of dialuric acid. Incubation of such red cells with small amounts of tocopherol makes them resistant to the hemolyzing effect of hydrogen peroxide, in complete analogy to the observations made on the red blood cells of rats deficient in tocopherol. This fragility of the red blood cells in newborn infants, indicating a "physiologic" vitamin-E deficiency, disappears slowly but is usually still present after five days. In contrast, in infants receiving supplements of tocopherol either directly (50 mg. daily) or via the mothers during the last weeks of pregnancy (150 mg. daily), the red blood cells lose their fragility by hydrogen peroxide about the fifth day of life. The fact that the effect of tocopherol in vivo is not as instantaneous on the red blood cells of newborn infants as it is in vitro on washed red blood cells seems to indicate either insufficient supply of vitamin E or the presence of protein fractions in the plasma that make tocopherol unavailable for the red blood cells, probably through the formation of a tocopherol-protein fraction.

The "physiologic" vitamin-E deficiency of the fetus and the newborn may have practial clinical implications in Rh-incompatibility, as well as in the development of erythroblastosis in newborn infants of diabetic and prediabetic mothers.

Splanchnicectomy for Pancreatic Fibrosis: An Analysis of Results in 24 Patients.
Dr. W. B. Ayers (by invitation), Dr. Daniel Stowens (by invitation), Dr. Alton Ochsner (by invitation), and Dr. R. V. Platou, New Orleans.

Partial sympathetic denervation of the pancreas was accomplished for 24 infants and children with mucoviscidosis six or more months ago. Justification for this operation was based on the hope that it might effectively interrupt a viscerovisceral reflex arc; cutting afferent fibers from the diseased pancreas might thus be expected to affect associated bronchospasm or bronchorrhea.

The patients operated upon were generally poor risks for any operative procedure. Twelve of them had far-advanced pulmonary manifestations, and 11 were considered to have moderately severe clinical features of mucoviscidosis. The near-simultaneous demonstration of the efficacy of aureomycin in therapy of this disease made final evaluation particularly difficult.

Results comparable with the encouraging effects observed in the first child of the series were noted in only two others. On the basis of our own observations, as well as those of parents and referring physicians, three patients were improved after the operation for appreciable intervals, late effects were equivocal in six patients, no changes of importance were noted in five, and one child could not be followed. Nine patients have died, one at operation, two after intervals of two and seven days, and the others two, three, five, six, seven, and 12 mo. following operation.

Gratifying though immediate responses appeared to be in five patients after paravertebral splanchnic block, use of this procedure was discontinued early in our series for technical reasons and because effects were so quickly dissipated. No criteria studied in our preoperative work-ups proved to have any value for judging later effects of splanchnic block or splanchnicectomy.

Splanchnicectomy is by no means a curative procedure for mucoviscidosis, though it may have a place in symptomatic management by helping to control distressing respiratory manifestations of the disease in some patients who have not responded to good medical, dietary, and antibiotic therapy. Our present observations do not permit any definite opinion regarding results of splanchnicectomy done earlier in life or in patients with milder manifestations of the disease; manifestations judged to be mild at the time of operation in a single child have remained unchanged for seven postoperative months, though she has received antibiotic therapy for most of this period.

DISCUSSION

Dr. Dorothy Andersen, New York: We have not been doing splanchnicectomies at Babies Hospital because the procedure did not seem logical; we were awaiting the results from New Orleans. I have to thank Dr. Platou for his prompt and frank report of the findings—for it is rarely a pleasure to prepare a complete analysis of a negative experiment.

After his report of three instances of possible improvement in a total of 24 operations, we may expect relief from the pressure on the part of referring physicians and referred patients to persuade us to do splanchnicectomies.

I should like to ask Dr. Platou one question. He said that there were certain circumstances in which splanchnicectomy might be useful; I should like him to define them more precisely, since practically all our long-term patients have long-standing bronchopneumonia or bronchitis.

DR. RALPH V. PLATOU, New Orleans: I think the main justification for the procedure is the possibility of relief of progressive respiratory distress characterized by bronchospasm and viscid sputum in patients who are not responding well to dietary, medical, and antibiotic therapy.

Chemotherapy of Disseminated Neuroblastoma in Children. DR. SIDNEY FARBER, DR. RUDOLF TOCH (by invitation), and DR. VIRGINIA DOWNING (by invitation), Boston.

At the 1940 meeting of the American Pediatric Society, evidence was presented for the modification of the almost hopeless prognosis given when a neuroblastoma was discovered. Ten of 40 patients then described were alive three to eight years after proof of the presence of such a tumor. In one of these, an infant with a neuroblastoma which was proved surgically and pathologically to have metastasized widely throughout the liver, a cure (now of 12 years' duration) was produced by the use of irradiation therapy. At the Annual Meeting of the American Academy of Pediatrics in 1948, the first evidence was presented of arrest and temporary disappearance of metastases throughout the skeleton in a child with a neuroblastoma which arose in the mediastinum. "Amino-an-fol" (4-aminopteroylaspartic acid), a folic acid antagonist, was the therapeutic agent responsible for the improvement, which lasted for about one year (S. F.).

During the past four years the tumor study group of the Children's Hospital has made observations on 52 children with neuroblastomas which had already metastasized at the time of observation by this group. Various chemical agents were employed in therapy, including folic acid antagonists, nitrogen mustard (methyl-*bis* or *tris* [2-chloroethyl] amine hydrochloride), and triethylene melamine, in some instances in combination with cortisone. All patients had received some irradiation therapy before chemotherapy was begun; all had responded poorly and were considered incurable or beyond benefit by irradiation therapy alone.

Detailed charts were presented concerning the various types of metastases, the combinations of therapy employed, the dose, and duration of treatment. Of 39 children in this series now dead, nine had definite changes attributable to chemotherapy either in the primary tumor or in the metastases; one patient had definite healing of the metastases to the bones and regression of the soft-tissue tumors in response to "amino-an-fol" therapy, while eight others showed temporary changes of important degree.

Of 13 children with disseminated neuroblastoma still alive, important changes have been produced in the tumors of nine. In three of these, definite regression of metastases to the skeleton with actual healing may be attributed to "amino-an-fol" treatment or to the action of triethylene melamine in combination with cortisone or "amino-an-fol." In six other children still living, important degrees of regression of soft-tumor masses or carcinostasis have been observed. These observations form part of the experience of the tumor study group, experience which during the past four years includes the use of chemical and hormonal agents as part of the total care administered to more than 700 patients with cancer incurable by surgical treatment or by irradiation alone. The survival in good health of one child 18 mo. after microscopic proof of skeletal metastases from a primary neuroblastoma of the adrenal gland gives further evidence that the practically hopeless prognosis given to patients with neuroblastoma up until recent years, even before metastasis had taken place, may be modified still further even in those instances of skeletal involvement in which survival was formerly spoken of in terms of weeks.

The proof that chemical agents may cause arrest and even disappearance of metastases to the skeleton and to the soft tissues from a primary neuroblastoma serves as justification for the acceleration of research concerning (1) the mode of action of carcinolytic agents; (2) the reasons for resistance of the tumor to such agents, and (3) the synthesis of new compounds which may be used as part of the total care of children with cancer presently incurable.

DISCUSSION

DR. WOLF W. BUELZER, Detroit: Dr. Farber's work serves as an inspiration for those of us who are trying to tackle the problem of malignant growths in childhood. I wish only to reiterate the emphasis on the care of these patients. We are often criticized for undertaking an apparently hopeless struggle. Some of our colleagues and many laymen consider our efforts an uncalled-for prolongation of suffering and agony.

There are two arguments to be made. One is the progress which has already been made. Although infinitesimal in view of the ultimate goal, it nevertheless justifies a moderate optimism and is also tremendously important from the investigative viewpoint. No one could have predicted a few years ago the striking, if temporary, reversal of the malignant picture that can be obtained in certain conditions with chemical agents. The implications of these findings are far-reaching.

The other point is not a scientific one at all, but has to do with the physician's attitude toward an incurable disease and with our approach to the family of the afflicted child. In this day and age the laymen frequently expect every effort to be made even when they have been fully informed of the hopeless nature of the condition. They can no longer be sent home with the cold-blooded diagnosis of malignant growth against which there is no remedy. It has been our experience, as I know it has been the experience in Boston, that in working intensively with this type of patient we are doing more than prolonging the agony. I am thinking particularly of leukemia, a condition in many ways similar to neuroblastoma. The diagnosis of the fatal, but more or less chronic, illness in a child places the family in a difficult situation in which they need help. Apart from the problems arising directly from the child's illness, the parents now become subject to many pressures: economic problems, pressures from friends and relatives, and their own subconscious guilt feelings which may end in mutual recrimination between father and mother and seriously disrupt the family. Such situations require a total approach, in which the physician must be specialist, family physician, financial adviser, psychiatrist, and father confessor, all in one. We have found that with this attitude we can create a feeling of satisfaction in the parents because they know that everything has been done, that they have contributed their active efforts, and that no stone has been left unturned, and because in the process they gain a deeper understanding of their problem. Our task is, of course, greatly facilitated by the fact that we are able to produce remissions and that the patients in remission can lead an essentially normal, active existence.

Quite apart from these considerations, the results of the present studies prove to be extraordinarily interesting, particularly the factor of fastness or resistance to therapy to which Dr. Farber referred. I wonder whether he would comment on his experience with the use of steroid hormones. In our relatively limited experience we have had the impression that the development of fastness can be delayed considerably by alternate types of treatment using the corticosteroid hormones. Since we have combined the use of these hormones in various ways with the administration of folic acid antagonists, we have been able to produce repeated remissions more and more consistently, and the remissions in the group given this therapy have lasted longer than those in the group of patients treated with "aminopterin" (4-pteroylglutamic acid) alone.

DR. IRVING J. WOLMAN, Philadelphia: I should like to say "me too" to everything that Dr. Zuelzer expressed and to the points Dr. Farber so well emphasized. I think every one owes a debt to Dr. Farber for having taken the leadership in this attack upon what has always been thought to be a hopeless kind of disorder.

If we lump the leukemias and sarcomas together, I think we must say that a great deal of help has been given to a great many patients by the following of a routine such as was outlined. The solution to the problem of the best therapeutic agent for control of malignant growth depends on the gathering of a great mass of data. Any malignant tumor, and leukemia itself, exhibits such a wide natural variation in its spontaneous course that one cannot draw exact conclusions and deductions from a small series of cases. One needs hundreds of cases in which these various forms of therapy have been used before an evaluation can be made. In view of the diversity of treatments that are available, one has to say to oneself, "If we are going to

do any good beyond the immediate care of the present patient, we should draw up a uniform program of treatment for all patients and stay with it so long as nothing significantly better is available." It is important for each clinic to take one of these routines of therapy and try to assess its value in such a way that the figures from that clinic can be compared with the figures from other clinics.

It is really remarkable that neuroblastoma can be arrested often by a vigorous attack. I should like to cite a recent case of an infant with extensive metastases to the liver, long bones, skull, and brain who was given intensive treatment. For about a year the child had a rather complete remission. The liver remained large but did not grow any larger; the child gained weight; the head decreased in size, and, until a chemotherapy-fast relapse began, the child was given an extra year of happy life.

DR. SIDNEY FARBER, Boston: Dr. Zuelzer emphasized the important part of the discussion, which is the total care of the child. The great advance in the discovery of new chemical agents that have an effect upon cancer temporarily has been far overshadowed in importance by the great interest which has been shown in the child with a hopeless malignant tumor.

It may be important to have one clinic study one compound for a time and another clinic study another. Dr. Wolman's point is a good one. We must have as objective a background as possible for the comparison of results; but may I add a pessimistic note concerning the tremendous amount of labor that is required to achieve such an end. Our group has been able in these past four and one-half years to give chemotherapy or hormone therapy as part of the total care to some 750 patients with disseminated malignant growth. Despite that fairly large number, our progress in interpretation of results has been extremely slow, except in the case of acute leukemia in which the endp oint alone helps one, or in the case of neuroblastoma in which there may be a rapid reduction in size of the tumor.

In the case of the lymphosarcomas, we have patients who have been cured for three to three and a half years now, with disappearance of the tumor; only chemical agents of the folic acid antagonist series were employed.

It would not be appropriate to go further into the matter of resistance, which has been considered by groups such as Dr. Poncher and his colleagues and others in this country. I think that the mechanism of resistance will be discovered to be bound up with something closely related to the cancer cell, which has nothing to do with either cortisone or corticotrophin, on the basis of present evidence.

Finally, I think that the evaluation of this form of therapy must be based on life history and biological behavior of these tumors.

Diagnosis of Adrenocortical Tumors: A Useful Chemical Test. DR. LYTT I. GARDNER (by invitation), Baltimore.

The Patterson-Allen blue color test as a laboratory adjunct in helping to differentiate between adrenocortical hyperplasia and certain adrenocortical tumors has been investigated. Its advantages are (1) reagents are simple and stable; only concentrated sulfuric acid and 95% ethanol are needed; (2) the test may be done on a small aliquot of the final alcoholic residue used in the usual urinary 17-ketosteroid determinations; hence no additional extraction is necessary; (3) the test distinguishes sharply between androsterone and dehydroisoandrosterone. The latter steroid is often excreted in large amounts by patients with adrenocortical tumors.

The test is performed in the following manner: 0.2 ml. of the alcoholic 17-ketosteroid residue is added to a small flask. This is evaporated to dryness on a steam bath, and to it are added 3 ml. of a reagent composed of one volume of 90% ethanol and four volumes of concentrated sulfuric acid. This is heated at 55 C. for 12 min. and cooled one minute in water; 4 ml. 95% ethanol is added. If positive, a blue or purple color develops. For specimens from normal persons or those with adrenal hyperplasia, a brown color develops. Our laboratory has adopted the practice of performing this test routinely on all specimens showing abnormally high 17-ketosteroid values.

By this technique characteristic absorption curves (350 μ to 800 μ) have been obtained on urinary extracts from patients with adrenal hyperplasia and adrenocortical tumor. Daily excre-

tion of dehydroisoandrosteronelike steroids in normal adults and in persons with adrenal hyperplasia (pseudohermaphroditism) has been found to be 0 to 9 mg. A patient with adrenocortical tumor excreted between 36 to 123 mg. a day. Data are presented concerning the urinary excretion of these steroids in patients with adrenocortical hyperplasia and tumor treated with cortisone.

DR. LAWSON WILKINS, Baltimore: I should like merely to emphasize one or two points that I think are of very great practical value in Dr. Gardner's paper. In the first place, I believe that the administration of cortisone to determine whether or not it depresses the total 17-ketosteroids is an easy and valuable test in the differential diagnosis between adrenal tumor and hyperplasia. In congenital adrenal hyperplasia cortisone in the proper dose always causes a marked depression of 17-ketosteroids. So far as we know, cortisone does not suppress the urinary ketosteroids in cases of tumors of either the adrenogenital or the Cushing's type. I believe this test may make it unnecessary to explore certain patients for tumor.

The second point is that it is becoming important to study the adrenal steroidal excretion qualitatively as well as quantitatively. Both in adrenal hyperplasia and in tumors we encounter wide variations and combinations of symptoms. These patients offer experiments of nature that cannot be reproduced in any animal in the laboratory. These patients offer us the opportunity to learn which specific steroids are responsible for various symptoms, such as salt loss, hypertension, and carbohydrate disturbances.

Up until now, and even at the present time, steroidal chemistry is very difficult. Chromatographic methods, countercurrent distribution, and various other methods are not available to every laboratory. The study of the spectrophotometric pattern of the Patterson-Allen blue color test, which Dr. Gardner has described, does not give us detailed information concerning all the steroids excreted, but nevertheless it may give us some important information in at least correlating some different patterns of adrenal steroids with different symptomatology.

Perhaps one of the most interesting points of Dr. Gardner's paper is the finding that the one patient with congenital adrenal hyperplasia for whom there was a slight hump in the curve at the 600-wave length differed from all the other patients in having hypertension. The method at least gives us clinicians a slightly handier tool for exploring problems of adrenal disorders than any we have available in most laboratories at the present time.

Experiences with Corticotrophin (ACTH) in the Acute Stage of Retrolental Fibroplasia. DR. FREDERICK C. BLODI (by invitation), DR. WILLIAM A. SILVERMAN (by invitation), DR. RICHARD DAY, and DR. ALGERNON B. REESE (by invitation), New York.

Between December, 1949, and March, 1951, corticotrophin (ACTH) was used to treat 31 infants with retrolental fibroplasia in the acute phase, with one failure; in two other infants one blind eye each developed. In the failure the disease had subsided after a three-week course; during renewed treatment of a subsequent exacerbation the infant died. This infant was treated at the first sign of retinal vascular change, according to a now abandoned policy of early treatment initiated in 1951. Thirteen infants were treated early according to this policy, and though the other 12 showed excellent improvement of the eyes, three died. Danger to the infant increases rapidly when treatment extends beyond two weeks.

During 1950 treatment was not begun until the following were observed: dilatation, tortuosity and new formation of retinal vessels, hemorrhage, and progressing, early, peripheral retinal detachment. In eight of 24 carefully observed patients the disease failed to progress; they were not treated and recovered. Sixteen patients with progressing disease were given a total of 20 courses of corticotrophin averaging 14 days a course, the best dose seeming to be 3.75 mg. per kilogram every six hours. Of these 16, none died, none are blind, and two have one blind eye each. There are 28 eyes with excellent vision and two with fair vision. In the two babies with one blind eye each vision in the other eye is better than fair; progress of the disease in the poor eye occurred subsequent to what had appeared to be a successful course of treatment with corticotrophin. During 1950 there were seven additional infants at Lincoln Hospital with disease who were not treated, either because of parental refusal or because the acute stage was missed. Six of these seven infants are totally blind.

A comparison of results at Babies Hospital, where there was the stated treatment policy during 1950, with those at Lincoln Hospital, where there was no treatment, shows the following for babies under 2,000 gm. birthweight: Babies Hospital: 134 infants not blind and two eyes (equivalent perhaps to one blind infant) blind; Lincoln Hospital: 66 infants not blind and six blind. Two patients at Lincoln Hospital are not included, since they were transferred to Babies Hospital, were treated, and recovered. Chi square is 6.1. During the years 1948-1949 at Babies Hospital there were also six blind infants among 118 survivors weighing 2,000 gm. at birth. The total incidence of disease at Lincoln Hospital (including all manifestations) was insignificantly less than that at Babies Hospital during 1950.

Since in addition to receiving corticotrophin, the infants with mild disease were also influenced by being cared for in 1950 instead of in 1948-1949, or by being resident in Babies Hospital in 1950 instead of Lincoln Hospital, no decision can be made as to whether the disease can be influenced by corticotrophin or whether it is subject to erratic, seemingly spontaneous alterations in severity despite a constant total incidence. A randomized case study within the same nursery is necessary to settle the question as to the value of corticotrophin.

Another point of interest observed in this study was a statistically significant inverse relation between birth weight and age at onset of detectable disease.

DR. WILLIAM E. LAUPUS, New York: I am very grateful for this opportunity to compliment Dr. Day on what may well be a very important contribution to this field, which I think is now our most serious problem regarding premature infants.

I should like to add also our experience with corticotrophin treatment of 13 infants. In this group we attempted to pick infants in whom we were almost certain retrolental fibroplasia was going to develop. The first two infants we treated had bilateral severe retinal detachments involving the retina almost completely in both eyes. Both of these infants were treated with 50 mg. of corticotrophin in four equal doses daily for a period of seven days. In neither instance was the disease in any way changed. In both infants the typical gray retrolental membrane subsequently developed.

Since then we have treated 11 infants for periods varying from 14 to 28 days, with doses varying from 12.5 to 25 mg. a day. In this group of infants we attempted, after reviewing our previous data, to choose those in whom we were almost certain the disease was going to progress to the fully developed condition. We picked a stage of early retinal detachment because in our previous experience approximately three of four babies who had arrived at this stage had gone on to the fully developed disease. In the fourth, of course, the disease spontaneously regressed, the detachment disappeared, and the eyes became normal ophthalmoscopically.

In this group of infants we had one total failure. This infant received 25 mg. a day for a period of 14 days and 12.5 mg. for an additional 15 days. We had three other infants for whom we could classify the result as fair. We have had two infants in whom there are residual evidences of minor temporal retinal detachment. There are five infants who have small amounts of fibrosis in the retina, but these scars should not interfere with vision.

On the basis of this experience, we feel that further work with corticotrophin is warranted. We have not had the experience that Dr. Day has had with serious illnesses in these babies. We have given prophylactic aureomycin in doses of approximately 50 mg. per kilogram per day. Despite this, three have had colds and one had a rather severe bronchiolitis, from which he fortunately recovered.

DR. EDWARD L. PRATT, New York: We have had a great deal of difficulty with this disease in Bellevue Hospital. About two and one-half to three years ago the incidence was very low in the nursery, and then, for no known reason, it rose for a short period; then for a year and one-half the incidence dropped to practically zero. It began to rise again, and last fall we decided to study these babies with use of corticotrophin.

From past experience we had found that Dr. Guy, our ophthalmologist, could predict very well in which infants retrolental fibroplasia would begin and eventually completely develop. In about 80 cases he had been wrong only once when he said the child would not get the disease. In about 30 cases he had been correct one-third of the time when he said they would.

Using this previous selection, we set up a study in which all associated factors were randomized. We thought about the ethics of the problem and from the reports that we received, we decided there was no sound evidence that we would be depriving any infant of certain treatment.

Since we have been treating infants on this basis, we have had four infants in the control untreated group, in none of which has the disease developed. We have had five in the treated group, and in four of these the disease has developed, about as severely as we would expect in the normal course of events; three have retrolental membranes and one retinal separation without membrane yet. Therefore, it is this problem of lack of uniformity that is bothering us.

It is true we are in a different geographical location, although in the same city. It is true that we are probably using a different batch of corticotrophin. That which we used we selected on the basis of having less posterior-pituitary extract in the combination than other lots. The daily dosage is about the same. The duration of therapy has been longer.

We do get all the physiological effects of the material, and some of the patients were made quite ill by it. Reduction in the rate of growth has been common. Therefore, we are at a loss to explain why, in our hands, we have not had good results. Perhaps it is the fact that we are working during an increase in incidence in our particular hospital, or perhaps it is the drug we are using, or perhaps it is some minor unassociated deviation in treatment that makes the difference.

DR. STEWART H. CLIFFORD, Boston: I have seen retrolental fibroplasia since 1936; at that time the diagnosis was made on discovering the membrane. Now much earlier stages of this condition are recognized on ophthalmologic examination. About one-half of the premature infants under 4 lb. (1,800 gm.) birth weight demonstrate early stages of the disease—but the disease regresses spontaneously in all but 15% of the cases. Even in those cases in which there is progression beyond this stage, there may be spontaneous regression, but frequently with visual damage—even though the membrane stage is not reached. Under these conditions it is obviously difficult to appraise the results of therapy.

In my experience a number of possible causes for this condition have been considered—light; deficiency in vitamin A; excessive vitamin A; oxygen; iron; water-soluble vitamins; vitamin E deficiency, and so on.

It is obvious we cannot compare incidence figures based on membrane development with those of series in which the diagnosis is made on earlier changes that may never go on to the full-blown disease. Therefore, we need an agreement on the ophthalmologic stages of the disease to make comparable analyses possible.

Dr. Day's contribution and leadership are very valuable—evaluation of therapy certainly in this instance requires the utilization of a control group. It is going to be possible under his direction to combine the material and experience of a number of clinics in various parts of the country in the hope that the cause and treatment of this distressing disease can be discovered.

DR. CLEMENT A. SMITH, Boston: We have had unexplained changes in the incidence of the full-blown condition in babies under 4 lb., from at least 20% during the two years which ended in 1948 to about 7% during the last two years. Such differences are somewhat of the order of those which have been reported.

We found about two or three months ago that when we reviewed the eight or nine cases in the Boston area in which cortisone or corticotrophin was used in treatment, there were such great differences in the time that treatment was begun and in the amount and form of treatment that no conclusions could be drawn, and for all intents and purposes, these infants might perhaps never have been treated at all.

We were recently persuaded by an enthusiastic colleague into treating another child with cortisone. That child within two days was in such a metabolic disturbance that we asked Dr. Nathan Talbot whether we should try to figure out some sort of parenteral electrolyte therapy which would bring him back to normal or should stop the drug administration and hope that the baby could get back himself. He said—I think a very good and characteristic answer—that when you give cortisone, you are disturbing the baby so close to the centers of metabolic regulation that you have no means of predicting what is going to happen and

advised us to "back out." So we did. Then we tried again, with half the dose, and produced a startling blood pressure increase and immediately stopped treatment again. (Incidentally, that infant has normal eyes, though only token doses were given which could have had nothing to do with the final outcome.)

Then we got in touch with Dr. Day, who has helped us a great deal by his very sane approach to the whole thing, which is characteristically modest, and by the fact that he has taken on his shoulders the burden of some of the unhappy effects of this drug. Considering Dr. Day's seeming successes and difficulties, we now feel that we can quite properly use his form of therapy on alternate cases, because we are offering a choice between what might be blindness and what might be something worse. We are embarked now on what I hope will be an alternate-case program, but I am sure that it will never be a perfect alternate-case program because of the supreme difficulty of telling which child will go on to permanent blindness untreated and in which child the disease will regress untreated.

My hope is that people will remember when tempted to treat infants with this drug that they are running certain risks. Actually, the only thing we do know at present about corticotrophin and cortisone in the treatment of retrolental fibroplasia is that the treatment is potentially dangerous.

DR. RICHARD DAY, New York: We were aware of the failure of corticotrophin in other institutions. What is the reason for the discrepancy in results in one institution as compared with another? As was said in the paper, our data show that there is a significant difference between two groups of infants with respect to incidence of blindness among all babies and also among those babies who had early signs of the disease. The better results were found in the babies for whom a certain treatment policy was pursued, and, with one or two exceptions, these infants were all in one hospital. Therefore, the cause of the different blindness rates could be the result of the treatment, or equally well from the data presented, a result of as yet unknown factors which are different in the two institutions where the study was carried out. In order to separate the possible causes, an alternate-case study should be undertaken. This we are now doing and should have done at the start. The question is not whether the figures are statistically significant; they are. The question which remains is whether the cause of the differences is corticotrophin or some other factor or factors.

There is one possible cause of the discrepancy between our experience and that mentioned by Dr. Pratt. In his cases corticotrophin therapy was begun very early. If my interpretation of Dr. Pratt's criteria for treatment is correct, infants treated early in this way would be already seriously enfeebled by corticotrophin at about the stage of the disease at which we begin the drug administration.

I agree with the comment that comparisons between institutions are made difficult by varying descriptive terms for the various stages of the acute phase of the disease, as well as for the end result. It is also true that the anatomical changes in the eyes cannot be correlated well with the amount of vision. A great need is for standardization of terms among ophthalmologists in this field. With such standardization of terms, comparison could be made on the basis of the number of surviving infants who are left with say five or six different categories of anatomical damage to the eye. This would be far more satisfactory than the classification of an infant as blind or not blind.

In closing, I want to remark that if our figures are to be explained by factors other than corticotrophin, then we are dealing with a disease which has significant variations in severity—a fact which one would hope would ultimately provide a clue as to the cause.

Metabolic Effects of Corticotrophin (ACTH). DR. J. A. JOHNSTON and M. J. SWEENEY (by invitation), Detroit.

Balance studies on children receiving corticotrophin (ACTH) for rheumatic fever, rheumatoid arthritis, and lupus erythematosus are described. Intake was varied with appetite, but the proportions of foodstuffs were kept constant.

The effect on nitrogen was a marked increase in the urinary output, but an increase in intake usually more than offset this, so that the balances sometimes became positive while the hormone was still being administered. In others the negative balance promptly became positive on withdrawal or reduction of dosage.

The nitrogen loss is felt by Albright to be the result of the action of protein-carbohydrate hormone (dehydro-17-hydroxycorticosterone), S hormone, but this is probably not adequate to explain it quantitatively; a diminished oxidation of glucose may be an additional factor.

The effect on calcium was not consistent. In four of five balance studies of sufficient length for significance, intake increased in three and diminished in one, fecal calcium increased in three and was unchanged in one, urine calcium rose in two, diminished in one, and was not significantly changed in one, and the balance increased in two and diminished in one. We doubt that the effect of corticotrophin on calcium in children is specific; our changes correlate better with intake than anything else, although increased stool losses regularly accompany depressed metabolism in hypothyroid children and can be promptly reduced with thyroid.

The basal metabolism fell in all cases. In one case the significant fall did not occur until the afterperiod. The drop in metabolism could be understood in part as a result of the nitrogen losses, though a phase of adrenal suppression following corticotrophin therapy is well recognized. In these children, however, the most important contributing factor would be the suppression of the disease process.

Lipid Nephrosis: A Ten to Twenty-Six-Year Follow-Up Study. Dr. William Obrinsky (by invitation), New Orleans, and Dr. Jerome L. Kohn, New York.

In previous communications we reported our observations on children over a 20-yr. period admitted to Mt. Sinai hospital with a nephrotic syndrome. In this communication we report on 12 patients followed from 10 to 26 yr. The patients were followed 26, 24, 23, 17, 16, 16, 12, 10, 10, and 10 yr. With one exception all the patients, we have reason to believe, are in good health. When last seen, the blood chemistry examinations gave normal results in all; two had increased blood pressure, and seven had albuminuria.

The most interesting patient was a woman followed 25 yr., who was 8 yr. old when first seen. During the first year of illness she had a typical course, with many episodes of recurrent infections, recurrent edema, and diuresis. Upon discharge there was improvement of her general condition; her blood urea nitrogen fell to within normal limits. During the next three years the amount of albumin in the urine gradually became less. At the age of 20 she married, and she was successfully delivered of two normal children, but during the last four months of these pregnancies toxemia with hypertension, albuminuria, and moderate blood nitrogen retention developed. Upon termination of these pregnancies her urine and blood chemical values returned to normal. She was found to have diabetes mellitus when 31 yr. old and was treated for this condition. The following year she again became pregnant. During the early part of the pregnancy she had diabetic ketosis. Six weeks prior to term she was delivered of a large, edematous baby which died soon after birth. Although there was an increase in blood pressure during this last pregnancy, there was no albuminuria.

She was last seen a few months ago when she was admitted to the hospital in diabetic ketosis. She was also found to have an acute psychosis. Unfortunately, we were unable to do an exhaustive kidney-function test, since it was necessary to transfer her to a mental institution. During the hospital stay it was noted that her urine showed a small amount of albumin, the blood pressure was normal, and her blood urea was also normal. A phenolsulfonphthalein test showed excellent excretion of the dye.

A second patient followed for 25 yr. was admitted at the age of 2½ yr. with nephrotic syndrome. During a long hospital stay his condition followed the usual clinical course. It improved after an attack of measles. The albuminuria persisted, however. When he was 14 yr. old, results of kidney-function tests were normal and an Addis count revealed many formed elements. He was rejected for military service during World War II on three different occasions. However, he was able to carry on his work as a salesman. Except for urinary findings and moderate hypertension, he is in good physical condition. We believe we can assume that this patient has good kidney function.

Another child was first seen when 4 yr. old. The disorder followed the usual clinical course. Two years after onset she had measles without any apparent effect on the course of the illness. When she was last seen after 16 yr., albuminuria was still present. She had a high degree of hypertension. Her blood urea nitrogen was normal. It was our impression, however, that she had a kidney involvement which was progressive.

Finally, a child was first seen when 2½ yr. old and was followed for 17 yr. During the first two years the patient had infections with Pneumococcus type VI on six different occasions. After an attack of measles, he showed some improvement for about two months. Two years after onset there were no clinical symptoms of kidney involvement. The child developed normally. There was no albuminuria, but moderate hypertension was present.

From our observations for a period of 26 yr. it is difficult to conceive that lipid nephrosis is a stage in the natural course of progressive glomerulonephritis, such as is seen after acute hemorrhagic glomerulonephritis. This is also borne out, we believe, in an examination of our postmortem material. If one should assume that lipid nephritis is primarily a kidney disease, does the improvement after measles, for example, mean an arrest or reversal of glomerular damage? Can one assume a reversal in true progressive glomerulonephritis? We have never seen complete recovery after intercurrent infection in a child with chronic nephritis. It is true that many children with the nephrotic syndrome go on to chronic nephritis, but certainly the course follows a pattern different from that seen after acute glomerulonephritis.

Thyroid Function in Young Children with Nephrotic Syndrome. Dr. Lee E. Farr, Dr. James L. Gamble Jr. (by invitation), Dr. Charles G. Foster (by invitation), and Dr. James S. Robertson (by invitation), Upton, N. Y.

Whether or not the thyroid is a normally functioning gland in patients with the nephrotic syndrome has long been a vexing question. Data which have been published from studies of the basal metabolic rate in these patients have been confusing and conflicting. Until the tests for thyroid function using radioactive iodine became available, no satisfactory objective means of testing thyroid function in this group of patients had been developed.

In the present investigation eight children ranging in age from 2 to 6 yr. were observed. All had been under study in the hospital, and at the time the iodine-uptake studies were done the patients represented a variety of states of the illness. Renal function ranged from 14 to 225% of normal; edema varied from mild to massive and incapacitating, and in some of the patients no edema was detectable clinically.

After eight days on a low-iodine diet, each patient was given 3 to 5 microcuries of I^{131} by mouth. The uptake by the thyroid gland was measured in vivo with a previously calibrated Geiger-Müller tube. Counts were taken at short intervals during the first 24 hr. and then daily for five days. In two patients it was possible to check the in-vivo estimations by tests on urine specimens, and good agreement was found.

In each instance the uptake of iodine by the gland was observed to be at a rate consistent with at least that of a normally functioning gland. The maximum uptake varied from 30 to 60% of the administered dose. From these data it was concluded that in young children with the nephrotic syndrome there is no impairment of the thyroid-gland function insofar as its ability to take up iodine is concerned. To establish definitely the normality of thyroid physiology in nephrotic children, additional information is necessary.

Lipid Nephrosis and Corticotrophin (ACTH). Dr. Benjamin Kramer, Dr. Samuel H. Silverman (by invitation), and Dr. Daniel Casden (by invitation), Brooklyn.

During the past year we have treated eight patients having uncomplicated lipid nephrosis with corticotrophin (ACTH). These patients were studied for periods ranging from one to four months, during which time the following laboratory determinations were done: sedimentation rate; blood count; urinalyses for albumin and formed elements; estimations of total serum cholesterol and ester, total lipids, serum calcium, inorganic phosphorus, and phosphatase, total proteins, albumin to globulin ratio, serum electrophoretic patterns, urea, blood carbon dioxide-combining power, chloride, sodium, and potassium; eosinophil count; blood-pressure reading, and body weight and temperature curves.

The dose of corticotrophin used was between 60 and 100 mg. per day.

A diuresis resulted in a majority of our patients between the fifth and twelfth days of therapy while the patients were receiving full dosage of corticotrophin. The total protein rose from a mean of 4.8 gm. per 100 cc. prior to treatment to 5.8 gm. after treatment. The greatest rise in protein was in the albumin fraction, the mean values increasing from 1.8 gm. per 100 cc. before corticotrophin therapy to 3 to 3.2 gm. after therapy. The serum cholesterol level, which ranged initially from 670 to 1,000 mg. per 100 cc., tended to return toward normal, although no value was completely normal. During the course of treatment the percentage of free cholesterol became abnormally elevated in three patients, one of whom displayed hepatomegaly. Serum potassium and sodium levels were not significantly affected. Serum inorganic phosphorus tended to fall, and serum calcium tended to rise.

The effect of corticotrophin therapy on the electrophoretic pattern of serum seemed to be an increase in the albumin spike and an unjumbling of the $alpha_2$ and beta globulins into individual peaks. Gamma globulin remained low, and the salt anomaly remained unchanged.

In the course of our investigations we observed the following side reactions to corticotrophin: hypertension, hepatomegaly, euphoria, increased appetite, and decreased resistance to infection. However, none of these seriously interfered with therapy.

Seven of the eight patients left the hospital free of edema. Four patients have remained edema-free one and a half, two, six, and six months, respectively. Three patients had recurrences of edema one, one and a half, and two months after discontinuation of corticotrophin treatment.

We have presented our cases so that they may be added to the ever-growing literature on this vitally important subject and perhaps help in formulating definitive theories on the mechanism of action of corticotrophin and cortisone in this disease.

Effect of Corticotrophin on Children with Nephrotic Syndrome: Clinical Observations on Thirty-Four Children; The Effect of Cortisone in Four. Dr. Milton Rapoport, Dr. Wallace W. McCrory (by invitation), Dr. Alexander J. Michie (by invitation), and Dr. Guilio Barbero (by invitation), Philadelphia, and Dr. Henry L. Barnett, Dr. Carolyn W. Forman (by invitation), and Helen McNamara (by invitation), New York.

The influence of corticotrophin upon 34 children with the nephrotic syndrome was studied in the period from August, 1949, to March, 1951.

I. *Influence upon the Components of the Nephrotic Syndrome.*—1. Edema: Corticotrophin induces a profuse diuresis on the first course in a highly significant number of children (82%). It can also cause diuresis repeatedly but not invariably in the same child. Failure to respond to a given course in a series does not preclude subsequent response. The total daily doses given at six-hour intervals ranged from 40 to 150 mg. and, while the drug was usually given for eight to 12 days, the duration of therapy ranged from five to 17 days. With the use of loss of edema as a criterion of effective action, it was found that 50 mg. daily was as potent as any higher dose. Diuresis resulting in delivery of edema fluid can begin on the fifth day or later and can begin while a child is receiving corticotrophin or as late as four days after cessation of therapy.

Neither the age of the child nor the duration of the nephrotic syndrome seemed to determine whether a child responded to corticotrophin treatment with a diuresis. Evidences of accompanying glomerulonephritis, hematuria, azotemia, and hypertension did not appear to influence the occurrence of diuresis.

2. Hypoproteinemia: Significant increases in serum protein concentration (Howe technic) were apparent only after edema had been lost on corticotrophin therapy.

3. Proteinuria: Diminution of proteinuria was observed frequently early in the course of corticotrophin administration. This may occur in the absence of diuresis.

4. Hyperlipemia: An increase in total serum lipid and cholesterol concentrations, similar to that evoked by corticotrophin in normal human beings and animals, may occur early in the course of corticotrophin therapy. Of greater interest is the decrease in hyperlipemia on corticotrophin administration, which may occur independently of accompanying or ensuing diuresis.

5. Serum Nonprotein Nitrogen: Rises to higher levels of initially elevated serum nonprotein nitrogen concentrations may occur early in corticotrophin therapy. With diuresis, elevated nonprotein nitrogen values fall to normal levels.

II. *Evidences of Increased Secretion of the Adrenal Gland Induced by Corticotrophin Therapy in the Child with Nephrotic Syndrome.*—1. Eosinopenia occurred regularly. Eosinopenia seems to be so sensitive an expression of adrenal-gland stimulation that it is not useful as a quantitative index of therapeutic adequacy of any adrenal-gland effect upon the nephrotic syndrome produced by corticotrophin.

2. Gain in weight due to sodium and water retention occurred in many of the children and in several produced such massive anasarca as to constitute a therapeutic hazard.

III. *Complications of Corticotrophin Therapy.*—1. Metabolic alkalosis with resultant tetany and associated hypokalemia occurred in two children; successful prophylaxis was obtained in other children by daily dose of 1.5 gm. of potassium citrate.

2. Infection, septicemia, spreading cellulitis, and peritonitis occurred in 10 children. Routine antibiotic prophylaxis is now employed during and after therapy.

3. Hypertension with tachycardia compelled cessation of corticotrophin therapy in five children.

4. Treatment for more than 14 days or closely repeated shorter courses of corticotrophin therapy may produce reversible changes characteristic of Cushing's syndrome.

IV. *Influence of Corticotrophin upon Prognosis of Nephrotic Syndrome.*—The status of 34 children in this study is as follows:

1. Six are dead of progressive renal failure: Two had no diuretic response to corticotrophin treatment; two had one response, and two had two responses.

2. Among 28 living children, (*a*) six were followed less than six months: four are in remission, and two have reaccumulated edema fluid after corticotrophin-induced diureses; (*b*) 22 were followed six to 18 mo.: (1) one child has been cured for 12 mo.; (2) 10 are in remission, eight after corticotrophin-produced diureses and two after spontaneous diureses; (3) 11 are edematous; six responded one or more times to corticotrophin treatment; two have failed repeatedly to respond to corticotrophin administration, and three who formerly had responded to corticotrophin treatment no longer do so. These three have advanced glomerulonephritis and renal failure.

In summary, corticotrophin therapy appears to alter those body responses which are manifest as the nephrotic syndrome without directly attacking the etiological agent that evokes these responses. It is a potent tool in the investigation of the nephrotic syndrome.

Five courses of cortisone were given to four patients as follows: three children received 75 mg. daily for six to 15 days, which produced no diuresis, and one child was given 100 mg. daily for 10 days.

DISCUSSION

DR. MITCHELL I. RUBIN, Buffalo: It was interesting to see the results of Dr. Kohn's long-term follow-up study of patients that had been observed for as long as 26 yr.

In regard to the question whether nephrosis is a renal disease or not, a discussion on that particular point could go on forever. In addition to what is already known, we have the following evidence presented during this meeting: The nephrotic kidney has a leakage of what seems to be normal serum protein, a condition which the normal kidney does not have, and corticotrophin decreases this leakage. Evidence of dysfunction elsewhere in the body does not mean that the etiological agent is not producing, in addition, or even primarily, disease in the kidney.

The question of using the term "nephrotic syndrome," of course, can be quite confusing. That so-called "lipid nephrosis" is a disease entirely distinct from nephrotic syndrome associated with glomerular disease may be questioned. In my mind, there is a distinction, and clinically they appear as different diseases. Certainly, it is extremely difficult to make the differential diagnosis when one first sees a patient with lipid nephrosis or the nephrotic syndrome of glomerulonephritis. We have seen patients with "classic" lipid nephrosis, as evidenced by all

tests, including clearances, who have gone on to die in uremia. Other children with the nephrotic syndrome of glomerulonephritis, as evidenced by hematuria and hypertension, we have rarely seen with complete recovery.

The term "cure," I think, has to be used in quotation marks. One child had evidence of renal disease followed by a period of "cure" which lasted almost eight and one-half years before nephrotic syndrome developed, and then he died in uremia.

I was happy to see Dr. Farr's data on iodine uptake. It gives me further strength in the conviction that there is no need for the tremendous doses of thyroid that are given to some of these patients. In my experience there has been no evident benefit from thyroid therapy.

One point not mentioned about corticotrophin therapy is its complications. The danger, for instance, of the washing-out of sodium, with the possibility of shock, in this type of therapy may be real.

DR. W. HEYMANN (by invitation), Cleveland: Has Dr. Kohn made the observation that some nephrotic children who appear to get well display orthostatic albuminuria? We noted it in three of 12 children that we examined five years ago. If one does not bear this possibility in mind, one will diagnose the condition of a nephrotic patient as persistence of the active disease when he may be suffering only from orthostatic albuminuria.

As far as the follow-up observations on a patient that went through pregnancy are concerned, we had a similar experience. We observed a girl who became pregnant 19 yr. after the onset of her nephrotic disease. It was severe at the time. She went through two pregnancies without evidence of renal disease. The combination of diabetes in one of Dr. Kohn's patients also is of great interest. In the nephrotic syndrome experimentally produced in the rat, diabetes induced by alloxan is astonishingly well tolerated.

Dr. Farr's paper is a valuable contribution, in that it eliminates a point of confusion that has persisted for several decades. His finding that there is no convincing evidence to prove thyroid dysfunction in the nephrotic syndrome is also in line with our experiences in the experimentally produced nephrotoxic disease in the rat. Removal of the thyroid or treatment with thyroxin does not alter the course of the experimental disease.

In regard to the corticotrophin studies, we have had similar experiences. We treated 20 persons with corticotrophin. Five showed complete failure to respond; 10 children experienced diuresis and had to be treated again and again. The remaining five went into a remission for as long as one and one-half years and may possible be cured.

We have also made the observation that corticotrophin treatment at times does, and at other times does not, have any effect in one and the same patient. The question of what this variation might be due to then arises. One possibility is the development of antihormones. That is unlikely because one can see in one and the same child, maybe two or three weeks later, that reaction to corticotrophin will occur. Development of antihormones also is unlikely because we have seen children fail to respond with eosinopenia when they received corticotrophin for the first time.

I was impressed by a paper given by Dr. Thorn in Cleveland recently, in which he stated that corticotrophin given intravenously in small doses over a period of eight hours was effective when its intramuscular administration had been ineffective. The intravenous use of this hormone will have to be studied in children that are refractory to its intramuscular administration.

DR. LAWSON WILKINS, Baltimore: Would Dr. Rapoport care to comment upon the relative effects of cortisone and corticotrophin? Also, does he have any remarks concerning the possible diuretic or antidiuretic factor of corticotrophin as used in this therapy?

DR. C. W. FORMAN (by invitation), New York: With regard to Dr. Kohn's paper, in experimental renal disease in rats we have been able to produce degenerative changes of the glomeruli with clinical symptoms of nephrotic syndrome by using large amounts of nephrotoxic serum. With smaller doses of the same serum we can produce proliferative changes similar to glomerulonephritis as seen in human beings.

DR. WILLIAM A. REILLY, Little Rock, Ark.: We have had an experience with nephrotic patients slightly different from that of Dr. Farr. Occasionally in the radioactive iodine-uptake

studies we get low normal values. Most of our uptake studies fell in the normal range, our normal values being the same as Dr. Farr showed; only rarely did we find uptakes in excess of the upper limit of normal. I do not know how to explain this discrepancy, and we shall certainly repeat our observations on other children, both normal and nephrotic.

We also tested our patients at various stages of their activity, that is, during relapse and remission. We could not determine any difference in the thyroid uptake or urinary excretion.

I am one of the group who do not believe that hypothyroidism is a main cause of this disease, although there is much evidence on both the pro and the con sides. I feel that the effect of thyroid substance in therapy is a diuretic one, perhaps, because of the speeding-up of circulation in the kidney, causing diuresis. This occurs only occasionally and usually after tremendous doses of thyroid substance. The nephrotic patient usually does not respond to ordinary doses of thyroid substance because he is not primarily hypothyroid.

Dr. Henry D. Lauson (by invitation), New York: I would like to limit my comments to the paper of Dr. Farr and point out, from the standpoint of the renal physiologist, that some of these data can be reconciled in terms of protein clearances. If protein-bound iodine is excreted as other proteins are, and, therefore, with a definite clearance, it would follow that the concentration of such protein-bound iodine in the blood should be low, as is the case, for example, with gamma globulin. Recently, in collaboration with Dr. Schulman in our department, our group has found a low iron-binding protein concentration in the serum of nephrotic children. The clearance of this protein was of a magnitude similar to that of albumin.

With relation to the activity or the increased uptake in the thyroid that Dr. Farr observed, I wonder if it might conceivably be explained entirely as the result of a high protein-bound iodine clearance.

Dr. Harriett G. Guild, Baltimore: Dr. Rapoport, has there been any histological examination of the kidneys of those patients who died in spite of treatment, and were any unusual lesions observed? Dr. Rich, in reporting his work on experimental nephritis in rabbits, although he was able to demonstrate an apparent suppression of glomerular lesions with both cortisone and corticotrophin therapy, also described, in a certain number of the cortisone-treated group, lesions that resembled the capillary glomerulitis of diabetes.

In the Harriet Lane Home, we have used cortisone in the treatment of the nephrotic syndrome, with encouraging results similar to those described with corticotrophin therapy. In one or two patients, however, in whom the glomerular process has been rapidly progressive in spite of temporary periods of improvement, we have wondered whether we could have introduced a new lesion that might actually be harmful.

Dr. H. L. Barnett, New York: I should like to comment also on the valuable contribution that was made by the long-term follow-up study of Dr. Kohn. It would be of extreme interest, in view of the question of cure of the nephrotic syndrome, if it were possible to do extensive kidney-function studies on this group of patients who had been followed carefully over a long period.

I would like to comment also, in view of Dr. Lauson's remarks on Dr. Farr's paper. Dr. Farr's approach to this problem is the only one which ultimately will answer definitively the question of the role of the thyroid in the nephrotic syndrome. As anticipated by Dr. Lauson, Kendall Emerson has an abstract in the current program of the Society of Clinical Investigation stating that the protein-bound iodine is low initially in some patients with the nephrotic syndrome and rises with corticotrophin treatment.

We would be interested in both Dr. Kramer's and Dr. Rapoport's present thoughts, in general, concerning the significance of corticotrophin at present in treatment of the nephrotic syndrome.

Dr. Jerome L. Kohn, New York: Dr. Barnett, in regard to orthostatic albuminuria, I can say only that in most patients the albuminuria was not orthostatic. I shall report on further observations, keeping this factor in mind.

Dr. Forman, it is almost impossible to predict the pathologic observations in patients that die early in the disease. A child was admitted to the hospital with typical acute hemorrhagic glomerulonephritis. The child was discharged apparently well. About two months later the

child returned with symptoms indicative of the nephrotic syndrome. The child died with complicating peritonitis. Histological examination of the kidney showed no glomerular change. There was no evidence of subacute glomerulonephritis.

Dr. Barnett, in regard to doing complete kidney-function tests on these persons who have been observed over a period of years, since they are in good health, it is difficult to obtain their consent for hospitalization. Some years ago Addis counts on five revealed an increase of formed elements.

Dr. Lee E. Farr, New York: During the past two years, I have had opportunity to see two patients with lipid nephrosis whom I followed 15 yr. after apparent recovery, at which time results of all functional tests were entirely normal. There was no protein in the urine. One of these, a girl now about 17 years old, went through puberty without event. At present, although I have not seen her recently, I understand from her physician that she has a low basal metabolic rate and is receiving thyroid.

In answer to Dr. Reilly, I have no explanation why differences might be encountered in his studies of iodine uptake and ours, unless perhaps there may be some age difference. Hill, Reiss, Forsham, and Thorn have reported (*J. Clin. Endocrinol.* **10**:1375 [Nov.] 1950) on some studies on corticotrophin treatment of a variety of patients, among whom were five adults with the nephrotic syndrome. Although their data are not given in detail, the basic metabolic rates and the iodine uptakes in this group were within the normal range. After corticotrophin administration there seemed to be a slight fall in both basal metabolic rate and iodine uptake. It is entirely conceivable that in the effect on persons of the older age group some differences may be found from that on the very young child.

I wish to point out that, before we gave the iodine, we placed the patients on an iodine-free diet for eight days. In our studies on other patients in the hospital with hyperthyroidism and thyroid carcinoma, we have found that this precaution is wise, because inadvertently a patient may receive enough iodine in the diet prior to the administration of the radioactive iodine to decrease uptake significantly.

In answer to Dr. Lauson's suggestion about the protein-bound iodine and its clearance, I can offer only speculation, which I think is probably idle at this time. These patients showed a great variation in their proteinuria, from a very low value to a very high value. One patient in particular had exceedingly severe oliguria preceding, during, and after the period of test with low renal function. Despite the low renal function and a presumed failure to excrete iodine, the uptake was not altered in any way.

I would like to ask a question about corticotrophin therapy and its evaluation by eosinophil counts in these patients. With the advent of corticotrophin, we have become interested in the eosinophil count of our patients. We have found that in many instances, for a protracted period, the eosinophil count may be exceedingly low, so that on the ordinary differential count where 100 cells may be counted, one or no eosinophils may be seen. However, these same patients, and others that we have observed, may from time to time have what, for convenience, we have called eosinophilic storms, when the eosinophil count inexplicably rises to very high levels, 15% of the differential smear. This may persist for weeks. Its appearance or disappearance did not correlate with any diuretic effects.

Dr. Benjamin Kramer, Brooklyn: I was pleased to see that Dr. Rapoport also observed a definite decrease in proteinuria preceding the onset of diuresis. Perhaps in this connection I might call attention to a paper presented by Dr. Lauson before the Society of Pediatric Research, in which he demonstrated the decrease of permeability of the glomeruli to protein after treatment with corticotrophin.

With regard to the relative merits of intramuscular versus intravenous administration of corticotrophin, we have had no experience with the effectiveness of various therapeutic routes of administration, but in the child whose condition did not respond to corticotrophin therapy, the failure was not due to lack of absorption of the hormone in spite of fairly high dosage. The eosinophil count dropped precipitously. If this is an adequate criterion, we would have to say that the corticotrophin is absorbed from the muscle when injected intramuscularly. However, it is possible that intravenous administration, by creating a higher concentration, might be more effective. Against that is the finding of Dr. Rapoport that a 100-mg. dose was no more effective than a somewhat smaller dose.

In regard to the future of corticotrophin in the therapy of lipid nephrosis, one would have to be very rash, I imagine, to prophesy, but there are a few questions that have occurred to us during the course of our investigation. Obviously, if Dr. Lauson is correct, corticotrophin exerts some specific effect upon the glomeruli. In just what way the glomeruli are affected, either morphologically or chemically, remains to be seen. Also, there is the consistent drop in plasma lipids and cholesterol. The fate of the lipids and cholesterol that disappear from the blood is also a question which requires further study.

Corticotrophin does afford at least temporary relief from the marked edema that is so embarrassing to the patient. Whether the actual duration of the disease is modified or the ultimate prognosis altered, only time will tell. The treated children seem to be no more susceptible to Streptococcus or Pneumococcus infection than the untreated children or those who, though treated, fail to respond with diuresis. This is also borne out by the persistence of low serum gamma globulin concentration in the electrophoretic pattern of the serum.

Long follow-up studies, such as that of Dr. Kohn, are, of course, of the utmost importance, particularly along with the morphologic studies of the kidneys in fatal cases. I imagine that further knowledge of the general effectiveness of corticotrophin will probably help us a great deal in understanding how much it can be expected to do for the nephrotic syndrome.

Book Reviews

Dental Caries: Clinical and Experimental Investigations. By T. Ockerse, D.M.D., D.D.S. Thesis submitted in partial fulfillment of the requirements for the degree of D.Sc. (Physiology) in the Faculty of Science, University of Pretoria. Price, 10.0 florins. Pp. 80, with 34 figures, 19 tables and 9 maps of South Africa. Issued by the Department of Health, Pretoria, South Africa, 1949.

The book consists of three major parts: a review of the literature, a clinical survey of caries and fluorosis in European children living in South Africa and experimental studies of caries in the rat.

The review of the literature extends over ⅓ of the book. It covers the subjects of tooth development, factors influencing tooth development, local causes of dental caries, experimental caries in rats and fluorine and dental caries. The review is extensive, but portions of it are not directly related to the later sections.

The clinical survey covers an astonishing number of examinations in 78,563 children. The caries incidence was higher in urban (93 per cent) than in rural children (79 per cent). The clinical studies of endemic fluorosis and caries confirm the findings reported by Dean and others in this country. An incidental finding—that caries is more prevalent in citrus growing areas—is of interest.

The author produced caries in the rat on a coarse particle corn meal diet similar to the one used by Hoppert and others (1931) and by Kellerman (1932). He found that boiled sweet potatoes and toffee candy added to the diet greatly accelerated the progress of decay, as did the addition of orange juice. The addition of meat did not affect the caries rate.

Neither sweet potatoes nor orange juice initiated caries in the rats on a fine particle corn meal diet, but the addition of sweets did. Five parts per million of fluorine in the drinking water did not reduce the caries incidence rate, but 100 parts per million had a marked inhibitory effect.

More caries developed in rats whose mothers were fed on a high carbohydrate, low protein diet during pregnancy and lactation than in rats whose mothers were fed a low carbohydrate, high protein diet. One hundred parts per million of fluorine in the drinking water of pregnant and lactating rats resulted in less caries in the offspring.

Similar results were obtained with highly-caries-susceptible rats which were inbred and subjected to the same experiments.

The chief value of this work lies in the experimental studies. A more thorough statistical evaluation of the enormous clinical data collected by the author might well lead to newer findings.

The Common Infectious Diseases: A Handbook for Students and Postgraduates. By H. Stanley Banks, M.A., M.D., F.R.C.P., D.P.H. Price, $4.50. Pp. 343, with 90 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1949.

This text is designed for students as a textbook on infectious disease, but it also contains a great deal of information of value to the practicing physician. Drawn from his experience over the past 20 years at the Park Hospital, London, and the City of Leicester Isolation Hospital, the material covers both the practical and the theoretical phases of infectious disease. A particularly good section is that which covers the immunology and epidemiology of scarlet fever. The modern concept of scarlet fever as one of many clinical manifestations of "streptococcosis," rather than a separate disease, is well outlined.

The section on whooping cough stresses the frequency of bronchopneumonia and the accompanying atelectasis. The necessity of repeated roentgenogram observations and the use of bronchoscopic and postural drainage for therapy are stressed. A separate chapter by Dr. L. J. M. Laurent on the electrocardiographic changes in the course of diphtheria is

excellent and stresses the frequency of electrocardiographic evidence of myocardial damage. Because of the low incidence of diphtheria in this country, many physicians are not aware of the necessity of looking for such changes before allowing the patients to resume physical activity.

The illustrations are generally good but, unfortunately, are not in color. References are up to date and include those of both an accepted and a controversial nature. This treatise can be well recommended to both undergraduate students and practicing physicians.

Théorie et practique de l'ostéosynthèse. By Robert Danis. Price, 1,100 French francs. Pp. 298, with 274 illustrations. Masson & Cie, 120 Boulevard Saint-Germain, Paris 6e, 1949.

This well published and profusely illustrated monograph is based on the author's extensive personal experience. Because Danis is convinced that all types of external fixation are harmful, he advocates open reduction for the majority of fractures. His three aims, which include no mention of function, are (1) immediate mobilization, (2) anatomic restoration and (3) "primary" healing without apparent callus (he considers "external callus" as pathological!). This means that surgery is performed even on easily reduced or undisplaced fractures.

The preliminary chapters include an excellent review of the general principles of first aid, preoperative selection and preparation of patients, postoperative care and follow-up. These are followed by a detailed description with illustrations of the anesthesia, the special radiographic technics employed, an ingenious type of molded splint, the fracture table and all the various instruments employed. The most interesting of these is a coaptation splint for producing and maintaining axial compression at the fracture site. This differs from the plate invented by Eggers in that fixation is rigid and the compression is obtained not by muscle pull but by the surgeon at the time the plate is applied. Danis insists on both points because he believes that absorption about the fracture ends is due not to aseptic necrosis but to lack of compression. For diaphyseal fractures of the femur Danis employs paired coaptation splints, which entails an operation of considerable magnitude.

The greater part of the book is devoted to a detailed description of technics and the numerous special instruments and pieces of apparatus which the author has devised. Many of them are masterpieces of mechanical ingenuity, but often the principles of engineering seem overemphasized and the principles of bone physiology slighted. For example, the author does not believe that bone grafts stimulate osteogenesis. He considers their effect as entirely mechanical and due to the immobilization they produce. Because of this, he makes extensive use of "os purum," a substance which has long been discarded by most orthopedic surgeons. The same lack of understanding of the process of aseptic necrosis and creeping substitution is evident in the section on femoral neck fractures. Danis is greatly concerned about the "softening" of the femoral head and the depression of articular surfaces which are often accompanied with extrusion of the nail. Since he attributes all these phenomena to insufficient fixation, he expects to correct the situation by changing the apparatus.

Those who read this book will disagree with much that it says, but they will be rewarded by several new ideas.

Bronchography. By Eelco Huizinga, M.D., and G. J. Smelt, M.D. Price, $15.00. Pp. 270, with 146 illustrations. Van Gorcum & Comp., Gironummer 2255, Aan den Brink, Assen, Netherlands, 1949.

This monograph deals comprehensively with a subject of somewhat limited interest to the medical profession in general. The chapter on the anatomy of the bronchial tree and lung segments is excellent, and the authors present a well merited plea for universal adoption of a standard system of nomenclature for this region of the body. Chapters on anesthesia for the procedure of lung mapping, roentgen anatomy, interpretation of the bronchogram, pathological bronchograms and the technic of bronchography as employed in Groningen University are among the principal chapters. The book is profusely well illustrated. A number of typographic errors detract slightly from an otherwise admirable work. The chief interest in this book will doubtless be found among bronchologists, thoracic surgeons and roentgenologists.

Die Erkrankungen der endokrinen Drüsen. By Prof. Dr. Med. et Phil. Adolf Oswald. Price, 58.00 Swiss francs. Pp. 580, with 44 figures. Hans Huber, Marktgasse 9, Bern 16, Switzerland, 1949.

This book is the work of one of the pioneers in the field of endocrinology. The author gives a comprehensive description of the functions of the various endocrine glands, their interaction and their relation to the autonomous nervous system and to the metabolic processes, including the function of the vitamins.

The manifold endocrine disturbances are classified according to their pathological genesis; their diagnosis is illustrated by excellent pictures, and the therapy is discussed in detail. Not less than 22 symptoms and syndromes are described under the heading "Diseases of the Hypophysis—Diencephalic System."

Literature is quoted in an overwhelming amount at the bottom of each page; thus, it is readily available and not disturbing to the reading of the text. A total of at least 3,500 references altogether are quoted from the literature published all over the globe, as far back as the end of the nineteenth century. The wealth of material given in this book makes it an invaluable source for everyone wishing to acquire information about and to improve his knowledge of the diseases of the endocrine glands.

The Vitamins in Medical Practice. By J. Shafar, M.D., M.R.C.P., D.P.H. Price, $4.50. Pp. 383. Staples Press, Ltd., 70 E. 45th St., New York 17, 1949.

This book begins by reviewing the chemistry and the physiological role of each vitamin together with the pathological conditions resulting from respective deficiencies. Subsequent chapters discuss the action of cooking on the vitamin content of foods and the role of vitamins in nutrition in infancy, childhood and pregnancy and for physical fitness, subjects of importance to the pediatrician. The last half of the book deals with the role of vitamins in disorders of the various systems and organs of the body, oral structures, gastrointestinal tract, liver, nervous system, skin, eyes, endocrine glands, hemopoiesis, and finally, rheumatic affections and infections. In relation to the last a chapter reviews the interaction of vitamins and chemotherapeutic agents.

An addendum brings the book up to 1949 by including information reported in 1948 concerning vitamins B_{12}, cobalt and folic acid in megaloblastic anemias, folic acid antagonists in the treatment of cancer, vitamins P and E in vascular disease, vitamin E in collagenoses and vitamin D in lupus vulgaris, together with its toxicity and the downward revision of vitamin C requirements. The bibliography, including the addendum, includes some 1,800 references. The subject index provides ready access to comprehensive information concerning the text.

Some Contemporary Thinking About the Exceptional Child. Proceedings of a Special Conference on Education and the Exceptional Child, November, 1949, Child Research Clinic of the Woods School. Reprint sent free on request to Charlotte E. Grave, Ph.D., Director. Pp. 64. Child Research Clinic, The Woods Schools, Langhorne, Pa.

These proceedings deal with a variety of subjects concerning the exceptional child.

One paper is entitled "Financial Provision for Public or Private Care of the Exceptional Child." This reviewer is unaware of the existence of any other paper dealing with this important subject. The problem of financing the care and education of the exceptional child is, to put it mildly, a serious one and is today complicated by rulings of the Commission of Internal Revenue. This involves consideration of income tax, trusteeships, gift taxes, endowments, annuities, medical deductions and so on. The facts presented should be of inestimable value to the parent of the exceptional child and to the school providing care for the child.

Other papers deal with the sociologic, psychiatric, medical (organic), psychological and educational problems of the exceptional child. An excellent discussion entitled "A Realistic Approach to the Exceptional Child" deals with the dignity of the "limited" child and protests against the false democratic principle that "all are created equal in intelligence and skill" because "such a philosophy does not give real opportunity to the exceptional."

This pamphlet should be read by pediatricians, educators, psychiatrists, and all who are responsible for the care, guidance and placement of the exceptional child, i. e., the one who deviates from the normal.

Die Eigenart der kindlichen Hirntaetigkeit. By Albrecht Peiper. Price, $7.55. Pp. 512, with 148 figures. Georg Thieme, Thomas Kirchhof 21, Leipzig C. 1 (Rusian zone), 1949.

This certainly is a unique book. The author has devoted more than 25 years to intensive studies of the functions of the nervous system of the child and of the not viable fetus, starting with or even before birth in the studies of immaturely born (premature) infants. During this time 116 papers have been published by the author and his associates on this problem.

The author's approach is based on experimental studies, with graphic recordings and exact clinical observations. He emphasizes the worthlessness of child psychology for this fundamental problem and also demonstrates that histological examinations of the central nervous system cannot be used to explain the functions and the development of the nervous system of the child as they can be for the adult. Utilizing the methods and principles of the work of Pavlov, Magnus and others in experimental animal physiology, the author has developed exact methods for recording the functions of the central nervous system of the child at all age levels.

There are 148 figures, the majority of them excellent recordings of sucking and respiratory movements of mature and premature infants under physiological and pathological conditions, such as in tetany, epilepsy, pertussis and anoxia. Photographs demonstrating the influence of the labyrinth on various reflexes and body movements at different age levels are very instructive.

Unquestionably, this book gives an enormous amount of objective information which can hardly be found anywhere else. Of course, knowledge of the German language is indispensable to make good use of the present edition.

Infant Nutrition. By F. W. Clements, M.D., D.P.H., D.T.M. Price, $4.50. Pp. 246, with numerous tables and charts. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1949.

This is a concisely written text covering several aspects of the fundamentals of infant nutrition. It is a capable compilation of selected facts and research reports on infant nutrition accumulated in the last 20 years. The author wrote this book primarily for the use of the pediatrician and nurse interested in the growth and development of the infant.

The first chapter deals superficially with some aspects of the physiology of tissue metabolism.

Part 2 consists of several chapters dealing with fetal nutrition. They cover the subject thoroughly. This is, perhaps, the strongest section of the book. However, in the chapter on vitamins no mention of vitamin B_{12} is made. This points up the observation that in this period of medical progress books become outdated before they reach their public.

This section involves much more detail than the average practicing pediatrician or pediatric nurse wants, nor will it necessarily interest them.

Part 3 deals with the composition of human and cow's milk and offers nothing new in this field. In the author's discussion of lowering the curd tension of cow's milk, he omits mention of the zeolite process of production of softkurd, or the predigestion of milk with enzyme addition.

Part 4 is a section on the physiology of the infant and records some of the generally known facts.

Part 5 covers the caloric and nutritional requirements of the infant. It appears that the vitamin D requirements are met mostly by sunshine in Australia, where the author lives, whereas in the United States more emphasis is placed on obtaining it by ingestion.

Part 6 is concerned with the application of the principles of infant feeding. It briefly surveys the methods of infant feeding and dietary supplements during the first year.

Very little space is given to the subject of deficiency disease.

Each section has a full bibliography.

This book should serve as an adequate reference book on infant nutrition, especially for medical students or infant nutritionists.

If You Have a Deaf Child: Collection of Essays by Individual Authors. Published for the Illinois Annual School for Mothers of Deaf Children. Price, $0.75. Pp. 134, with scattered sketches and photographs. University of Illinois Press, Administration Bldg., Urbana, Ill., 1949.

This booklet organizes the important material relating to the complex problems of understanding, rearing and beginning the education of the preschool deaf child with whom communication through hearing is difficult, if not impossible. The subject of the deaf child is covered in three sections: (1) training of children in general, (2) training of deaf children in particular and (3) schools, agencies and publications.

The first section includes discussions by a pediatrician, a nursery school worker and a child psychiatrist on the physical, intellectual and emotional development of "normal" children. It emphasizes the fact that the deaf child is a child first and always. Behavior to be expected of all children is outlined.

The second section covers specific points made by an otologist, an audiologist, a language specialist, a clinical psychologist and a teacher of the deaf. Structure, function, disturbances of the ear, hearing aids, development and training of speech patterns, emotional pitfalls and technics of home training are outlined.

The choice of schools and related agencies and a helpful bibliography comprise the final section. A modified preface by a well known mother of a deaf child presents a mother's point of view with dramatic eloquence.

There can be criticism of certain concepts of "child psychology" and of individual items relating to the use of hearing aids, yet, in all, the booklet admirably fills an overwhelming need. Though composed of individual essays, it is cleverly edited so that the continuity is maintained. The language is simple but not patronizing. Format, illustrations and printing are pleasant, even entertaining.

"If You Have a Deaf Child" is recommended to all parents of hearing handicapped preschool children. Otologists, pediatricians, psychologists, educators of the deaf and school teachers will find in it information specifically and generally helpful.

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[1] *References on request*

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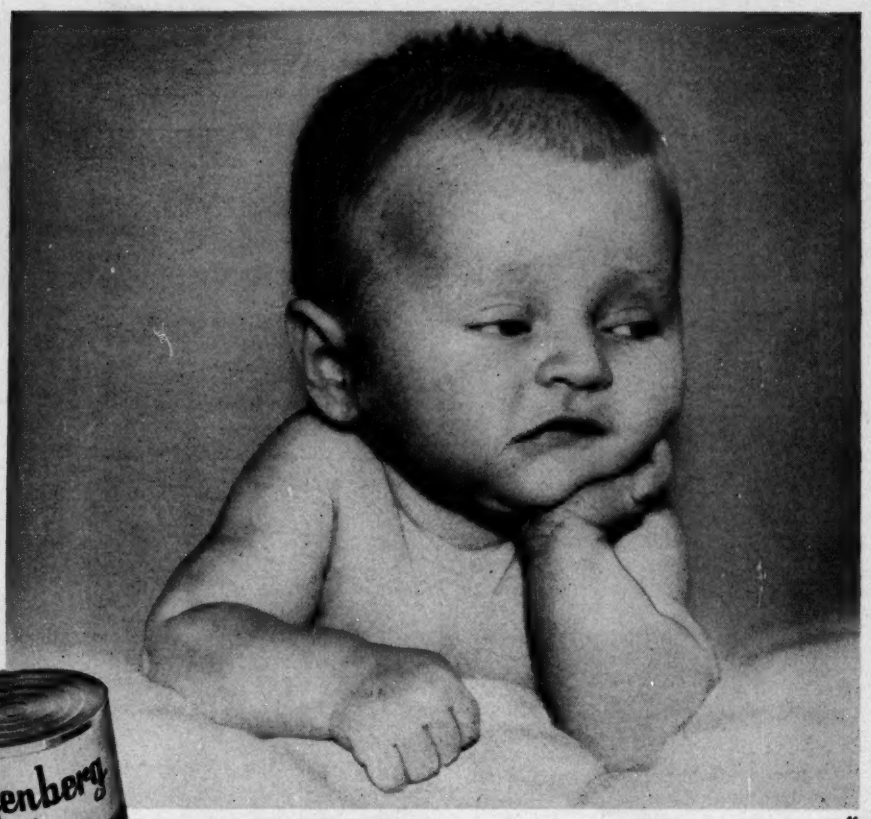

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[1] *Gamble, J. A.; Ellis, N. R. and Besley, A. K., U. S. Dept. of Agric. Tech. Bull. No. 671, page 61, (March 1939.)*

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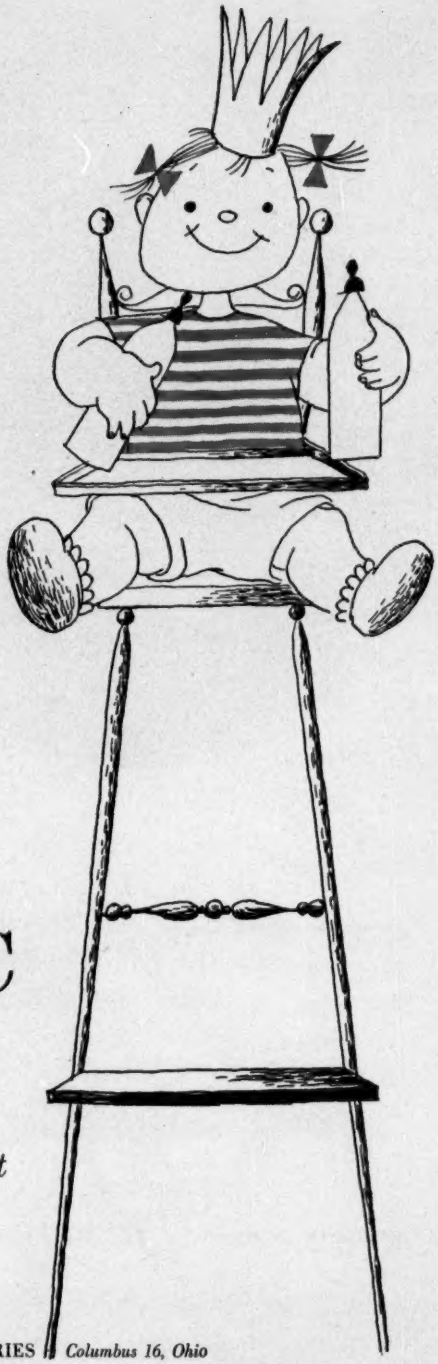

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Findings such as these and the fact that human antibody globulin is a highly complex protein containing all the essential amino acids justify the following authoritative deductions[6]:

a. Lacking an adequate supply of essential amino acids, the body manufactures antibody globulin with difficulty, and

b. Because of depleted protein reserves and inadequate intake of essential amino acids, persons long and seriously undernourished manifest increased susceptibility to infection due to inability to fabricate new supplies of antibody globulin.

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---

1. Cannon, P. R.: The Importance of Proteins in Resistance to Infection, J. A. M. A. *128*:360 (June 2) 1945.

2. Strumia, M. M., and Boerner, F.: Phagocytic Activity of Circulating Cells in the Various Types of Leukemia, Am. J. Path. *13*:335 (May) 1937.

3. Mills, C. A., and Cottingham, E.: Phagocytic Activity as Affected by Protein Intake in Heat and Cold, J. Immunol. *47*:503 (Dec.) 1943.

4. Elman, R., and Cannon, P. R.: Protein Malnutrition, in Jolliffe, N.; Tisdall, F. F., and Cannon P. R.: Clinical Nutrition, New York, Paul B. Hoeber, Inc., 1950, chap. 7, p. 192.

5. McLester, J. S.: Nutrition and Diet in Health and Disease, ed. 5, Philadelphia, W. B. Saunders Company, 1949, p. 347.

6. Cannon, P. R.: Recent Advances in Nutrition with Particular Reference to Protein Metabolism, Lawrence, Kansas, Univ. of Kansas Press, 1950, p. 19.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

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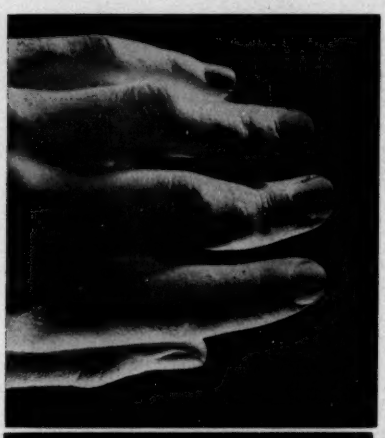

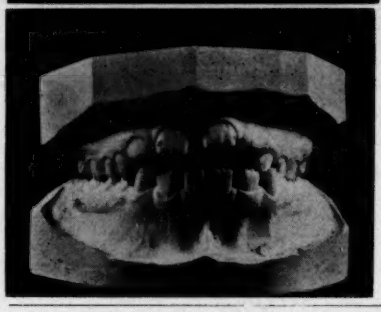

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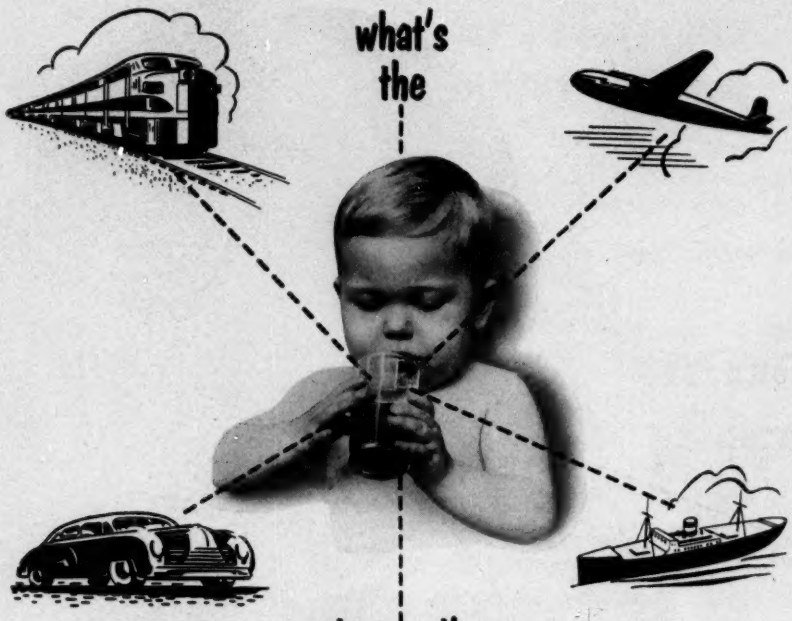

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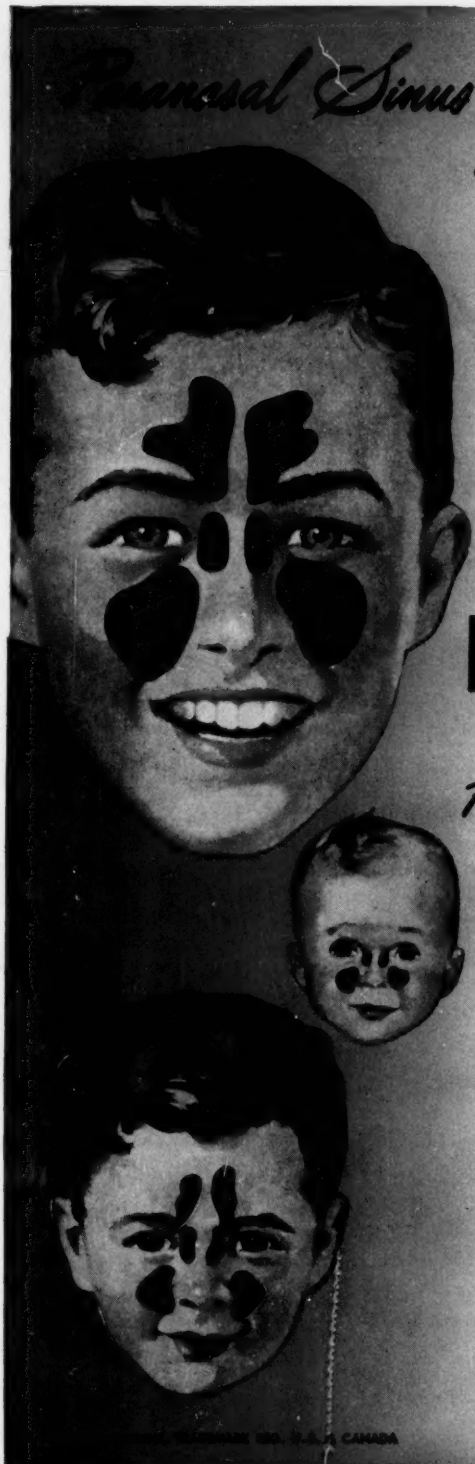

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— Burgess, T. S.: Jour. Med. Assn. Georgia, 37:44, Feb., 1948.

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